SURGERY
GYNECOLOGY AND OBSTETRICS
An International Magazine, Published Monthly

VOLUME 81 OCTOBER, 1945 NUMBER 4

II. THE VALUE OF THE VAGINAL SMEAR IN THE DIAGNOSIS OF UTERINE CANCER

A Report of 1015 Cases

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EARLY, accurate diagnosis of cancer of the female genital tract has long been the goal of gynecologists. Ewing (3) states that in 1931, 14,464 women died of cancer of the uterus, or 12 per cent of all cancer deaths were due to this one type. This is exceeded, in frequency, only by carcinoma of the stomach. Ewing arrived at figures of an average of 10 per cent approximate 5 year cures for uterine cancer. He calculated that the possible cure under ideal conditions, i.e. intelligent public, skillful and experienced specialists, and modern equipment, would be 40 per cent. The discrepancy between the possible rate of cure and of actual cure bears a direct relationship to the time at which diagnosis is established and treatment instituted. We feel that the vaginal smear technique for diagnosis of uterine malignancy is a definite forward step in the early recognition of the disease.

In 1943 we (2) reported 220 cases studied by vaginal smear for cancer. This report confirmed the previous findings of Papanicoloau and Traut as to the value and accuracy of the vaginal smear as an aid in the diagnosis of uterine malignancy. Since our last paper we have studied an additional 795 cases, making a total of 1,015 cases studied by this method, with a total error of 4.0 per cent. The patients for this study came from the Vincent Memorial wards and the Tumor Clinic of the Massachusetts General Hospital, and from the private practices of several physicians.

From the Vincent Memorial Hospital (the Gynecologic Service of the Massachusetts General Hospital) and the Departments of Gynecology and Medicine of the Harvard Medical School.

NEGATIVE CASES

Of the 1,015 patients 861 showed no evidence of cancer. Of these 36 per cent had biopsies, either of the cervix or of the endometrium, or the whole uterus was removed. These proved negative diagnoses are listed in Table I.

In addition to those shown in Table I our negative group also includes 48 negative postoperative and 89 negative postradiation patients (Fig. 1). These women had proved malignant growths of the uterus treated either by x-ray, radium, or surgery, and are now clinically well. Also included are negative cases, patients who did not present enough evidence for malignant disease to require

operative procedures. In this series of 861 negative cases 25 mistaken positive diagnoses were made by vaginal smear. These we regard as mistakes, since repeated biopsies were carried out in all cases and in none was microscopic evidence of tumor found. This represents an error of 2.9 per cent in "negative called positive." These mistakes will be discussed in a later paragraph.

POSITIVE CASES

In this series of 1,015 cases 154 were shown to have cancer on microscopic section. The positive cases and their pathologic diagnoses are shown in Table II. Of these 154 positive cases (39 endometrial and 109 cervical cancer) 16 cases were incorrectly called negative by vaginal smear. This is an error of 10.3 per cent (see Fig. 2). Of these mistakes eight were in the endometrial and eight in the cervical cancers.

The mistakes in this group of cases fall into two categories. The first includes smears in which cancer cells were present but were not seen on the original examination of the slide. On review of these smears the cancer cells are so obvious that there could have been no question of interpretation. These cells were missed because every field was not examined. Seven of 16 mistakes were of this type. The second group are those in which no cancer cells were found, even after the slides were reviewed. We must assume that in these 9 instances malignant cells did not exfoliate, or that degeneration of the malignant cells had occurred. We are including these in our mistakes. They actually present a limitation inherent in the method. Of these 9, 6 are from cases with endometrial cancer. The fact that cells from endometrial carcinoma frequently fail to appear in the vaginal secretion explains the lower diagnostic accuracy evident in this group.

We will review briefly the criteria for the recognition of cancer cells in the vaginal secretion. More extensive descriptions, including technique and staining, may be found in the monograph by Papanicoloau and Traut or in our previous publication (2). The basal cells are round or oval cells with green cytoplasm and an active vesicular nucleus. These cells may vary in size. The second group is the precornified. These cells are larger and more transparent than the basal cells and have a smaller vesicular nucleus. The third group is the cornified which are similar to the precornified except for an acidophilic cytoplasm and a pyknotic nucleus. Endometrial cells are encountered occasionally in the vaginal secretion. These cells are very small and have a small vesicular nucleus with very little cytoplasm.

Malignant cells show a good deal of variation, much more than is seen in the histological section of the same tumor. The cells shedding from an epidermoid cervical cancer are of two types, depending on whether the tumor itself shows any differentiation. The differentiated cells show extreme variation in size and shape. They may be extremely elongated resembling very closely a muscle fiber cell except for the long hyperchromatic nucleus. They may be rounded at one end with a long tail—the tad-pole cell. The differentiated cells have an adequate amount of cytoplasm but it is abnormally distributed.

The characteristics of the undifferentiated cells are as follows: (1) they occur often in groups; (2) the nuclei, which are hyperchromatic, show marked variation in size even to 100 per cent; (3) the nuclei stand out against a homogeneous background of cytoplasm in

TABLE I.—PROVED NEGATIVE CASES

	Cases
Chronic cervicitis	106
Polyp	36
Endometrial hyperplasia	13
Fibroids	76
Endometriosis	6
Miscellaneous	9
Adenomyosis uteri	2
Atrophic endometrium	3
Secretory endometrium	13
Proliferative endometrium	26
No evidence of malignancy	27
	317

TABLE II.—POSITIVE CASES

Epidermoid carcinoma of the cervix	90
Recurrent epidermoid carcinoma of the cervix	11
Adenocarcinoma of the cervix	6
Adenoacanthoma of the cervix	2
Adenocarcinoma of the uterus	27
Recurrent adenocarcinoma of the uterus	4
Adenoacanthoma of the uterus	8
Carcinoma of the vagina	6

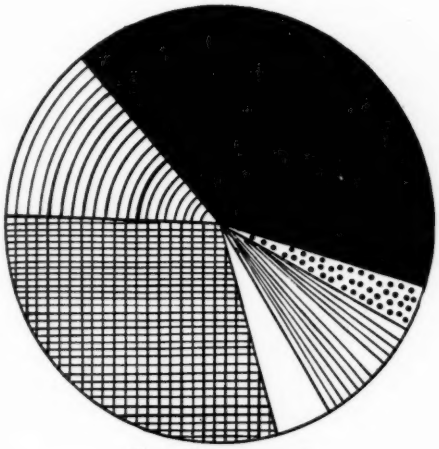

Fig. 1. Negative group.

Positive 13.5 per cent
Clinically negative, 40.0 per cent
Post radiation, 8.7 per cent
Postoperative, 4.7 per cent
Pathologically negative, 28.7 per cent
Mistakes, 4 per cent

which cellular borders are often indistinct. If single cells are encountered, an increase in nuclear size in relation to cytoplasm is the most important diagnostic aid. Adenocarcinoma of the cervix also shows cells of this undifferentiated type.

The diagnostic criteria for endometrial cancer are similar to that for undifferentiated cervical cancer. The cells have large nuclei with little or no cytoplasm. The cancer cells from endometrial cancer are more likely to be present in clumps with the cells in a dense mass. The size variation of the nuclei is not as great as seen in cervical cancer.

In reviewing our mistakes in the group "negative called positive" (false positive) we have found certain cells, probably histiocytes, which often give trouble in making the correct diagnosis. In our 25 mistakes, 8 were incorrectly diagnosed positive because of the presence of these cells. There are 3 types of histiocytes. The first and most familiar is a large cell with vacuoles containing ingested material, such as red blood cells and leucocytes. These are easy to recognize and are not the source of trouble. However, the next two

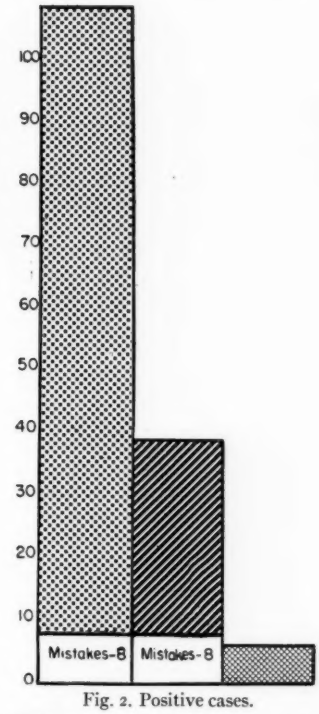

Fig. 2. Positive cases.

Carcinoma of the cervix, 109 cases
Carcinoma of the fundus, 39 cases
Carcinoma of the vagina

groups have proved to be very misleading. One group comprises the foreign body giant cell.[1] These are very large cells with sometimes as many as twenty nuclei. The nuclei are apt to have a characteristic peripheral arrangement (Fig. 3). Occasionally, however, there may be so many nuclei that they occupy the whole cell. These foreign body giant cells may be interpreted as malignant giant cells, if careful attention is not paid to the regularity in size of the nuclei and the adequate amount of cytoplasm present. These foreign body giant cells contain many nuclei which do not vary in size appreciably, while in the malignant giant cell the nuclear size varies a great deal. The

[1]Dr. Shields Warren has pointed out that foreign body giant cells are not seen microscopically in sections of the uterus and that probably what we are calling foreign body giant cells are groups of nuclear aggregates in hyalin or mucus.

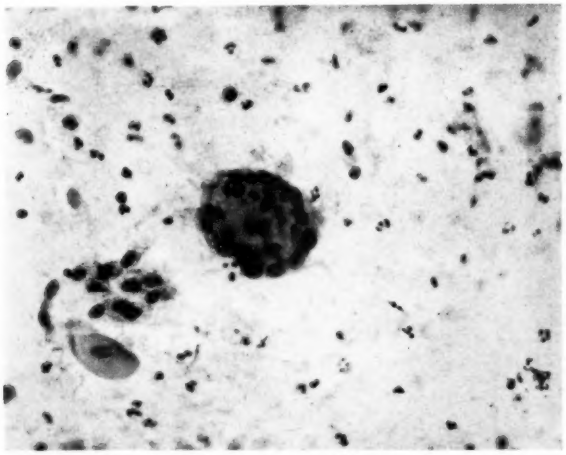

Fig. 3. A foreign body giant cell with peripheral arrangement of nuclei and small variation in nuclear size.

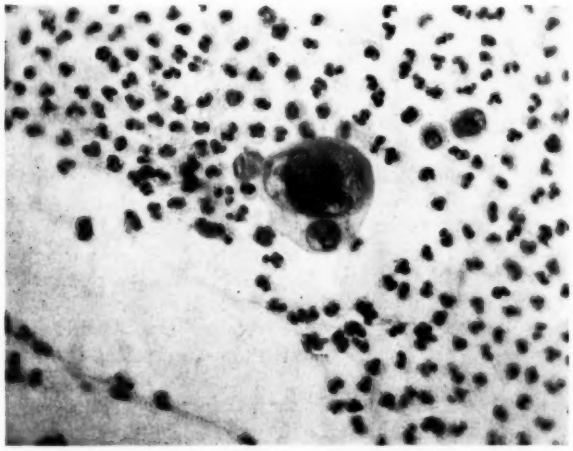

Fig. 4. A multinucleated malignant giant cell with central arrangement of nuclei and variation in nuclear size.

nuclei of the cancer cells stain much more deeply than those of the foreign body giant cells. In the malignant giant cell, the nuclei usually fill the entire cell, so that only a thin rim of cytoplasm remains visible. The difference between the two types of cells can be readily seen in a comparison of Figure 3, which demonstrates a foreign body giant cell, and Figure 4, which demonstrates a malignant giant cell.

A third type which leads to confusion is the small single histiocyte without ingested material. These cells often occur in groups and are then apt to be mistaken for undifferentiated cancer cells. Figure 5 shows such a group. Occasionally a group is found which is phagocytosing an epithelial cell, and in this instance it is easy to classify such cells as histiocytes. Other groups are much more difficult to interpret. There are three criteria

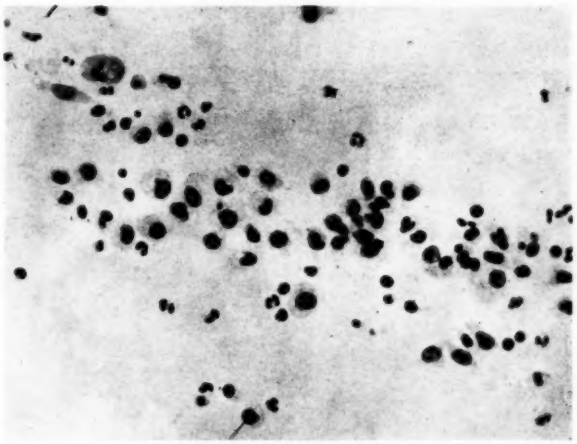

Fig. 5. A group of small, single histiocytes, showing characteristic foamy cytoplasm of the cells.

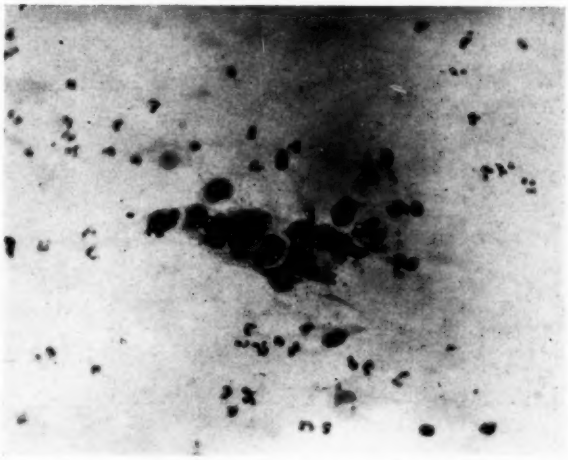

Fig. 6. A group of undifferentiated cancer cells, showing great variation in nuclear size.

for differentiating small histiocytes from cancer cells. The most important one is that the small histiocytes have a foamy vacuolated cytoplasm which is absent in the malignant cells. Second, the nuclei of the histiocytes do not vary markedly in size; and finally, the entire cell is smaller than the undifferentiated cancer cell. Compare Figure 5 with Figure 6.

In 2 cases in the negative group false positive diagnoses were made because of the presence of normal endometrial cells which were mistaken for cancer cells. The reason the endometrial cells prove troublesome is that their nuclei are hyperchromatic and there is very little cytoplasm. Since malignant cells have hyperchromatic nuclei and little cytoplasm, the reason for the difficulty is readily seen. However the cytologist should remember that nuclei of undifferentiated malignant cells vary a great deal in size. This is not true

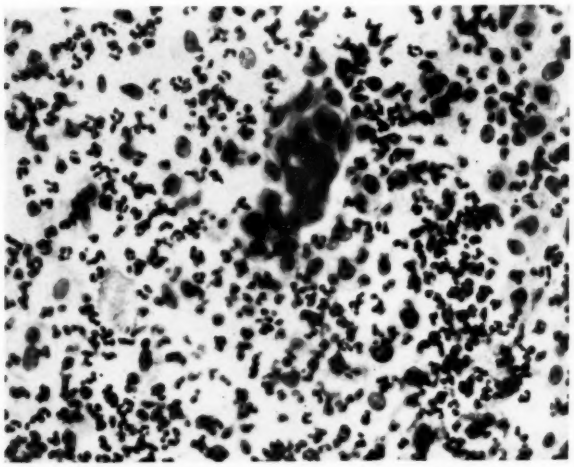

Fig. 7. Smear showing a group of aberrant basal cells in the center of the field.

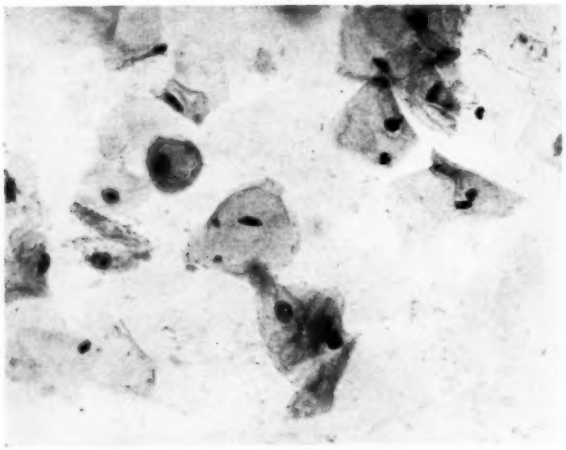

Fig. 8. Same as in Fig. 7, after administration of stilbestrol.

of the endometrial cells where the nuclear size variation is small. It is important to remember that when there is bleeding from the endometrium normal endometrial cells are often encountered.

Another type of cell which has caused some confusion is the atrophic cell of the basal layer of the vagina. When a vaginal smear is composed entirely of basal cells, aberrant forms are often encountered which are not easy to classify. These cells account for 8 mistakes in the group of "negative called positive." We have found that a satisfactory solution to this problem is to change the vaginal epithelium from atrophic to cornified by the administration of stilbestrol (1 mgm. per day for 10 days) as originally suggested by Papanicolaou. The basal cells will be completely replaced by cornified cells and at the end of the stilbestrol treatment the confusing atrophic

cells will have disappeared. A comparison of Figure 7 and Figure 8 represents this change.

The 7 remaining mistakes in the "negative called positive" represent smears which on reexamination still show, in our opinion, malignant cells. Two of these women have had hysterectomies for fibroids and no cancer was found. The remaining 5 have had biopsies only, and in 1 case the biopsy specimen was unsatisfactory. We have no explanation for this discrepancy other than to postulate that perhaps a small tumor may have been missed at the pathological examination. In our previous paper we reported a case in which no cancer was found by the pathologist on routine examination, but cancer was demonstrated after many subsequent sections were cut and examined. Te Linde, in a discussion of this very problem, reports 11 cases of early cervical cancer. He says "In approximately half of the cases several well trained gynecological pathologists were unwilling to make the diagnosis of cancer from the changes noted in biopsy specimens . . . . in all instances [after operation] the entire cervix was cut into blocks and in many cases much careful searching had to be done before an area of actual invasion was found."

DISCUSSION OF CASES

To illustrate the value of the vaginal smear in the early diagnosis of cancer, we are abstracting 8 cases diagnosed primarily by vaginal smear. Two cases represent endometrial cancer, 5 cervical, and of the 5 cervical cancers 3 are carcinomas *in situ* of the cervix.

M. H., M.G.H. No. 401600, aged 50 years, octipara, was admitted to the hospital in May, 1943, for contact dermatitis. In March, 1944, she was readmitted to the psychiatric ward because of generalized nongenital pruritis. Two aunts had died of cancer. She had the menopause in 1942. In March, 1944, she had an episode of vaginal bleeding which lasted for 4 days. In May, 1944, a vaginal smear was reported positive. Report on gynecological examination was: "The cervix is clean and a little red. There is no evidence of polyp or tumor." Four biopsies of cervix showed epidermoid carcinoma, grade II, of cervix. A Wertheim hysterectomy was done.

V.F., M.G.H. No. 284325, aged 47 years, quadripara. In January, 1941, patient had a carcinoma of the ovary removed. There was a metastasis to the right transverse colon. A right colectomy was performed in February, 1941. In March, 1941, the patient received 1400 r to the pelvis. The patient was well until September, 1943, when she noticed some vaginal spotting. No vaginal smear was taken at this time. In February, 1944, a vaginal smear was reported positive. A total hysterectomy was performed. The pathological report was papillary adenocarcinoma. Note: "tumor is very suggestive of primary fundal carcinoma rather than metastasis from the ovary. However, in a few areas the morphology is similar to that observed in the peritoneal implantation removed in 1941."

N.O., M.G.H. No. 338280, aged 51 years, tripara. In October, 1941 the patient was found to have epidermoid carcinoma of the cervix, grade II. She received the usual x-ray and radium treatment. On routine follow-up in the Tumor Clinic (March, 1944 to September, 1944) she had repeated positive vaginal smears. No cancer could be found on clinical examination. Tissue from the vaginal vault, obtained under anesthesia with great difficulty, showed carcinoma of the cervix.

A.B., M.G.H. No. 444002, tripara. The patient was seen on December 4, 1943. One sister had carcinoma of the cervix. The patient had had the right ovary and a portion of the left ovary removed at an operation 18 years before. Menstruation had ceased at that time. One year ago over a period of a week she had noticed vaginal spotting. No subsequent bleeding or spotting occurred. A vaginal smear was positive for cancer.

The pathologist described material obtained at biopsy of the cervix as follows: "the epithelium in one small area shows slight atypicality slightly suggestive of carcinoma *in situ*. The specimen, however, is inadequate to warrant a positive diagnosis. On January 13, 1944, a second biopsy was done. Specimens were removed as close as possible to the area of the previous biopsy. Pathological diagnosis of this material was "chronic cervicitis, epidermitalization of cervical glands, precancerous."

A total hysterectomy was done on March 3, 1944. Pathological diagnosis: epidermoid carcinoma *in situ* of the cervix.

H.A., M.G.H. No. 441482, aged 49 years. When first seen on June 20, 1938 the patient reported that for 2 months she had noted daily spotting. A biopsy specimen was reported as acute and chronic cervicitis. The patient was seen for the second time on March 7, 1944. The periods were regular. She was having hot flashes. The cervix was found to be lacerated and open. She was bleeding from the os (? catamenia). A vaginal smear was taken on March 7 and was positive for cancer. A biopsy specimen taken on March 18 was reported as a question of carcinoma *in situ*. A complete hysterectomy was done. Final pathological diagnosis was carcinoma *in situ* of the cervix.

E.T., M.G.H. No. 439369, aged 46 years, tripara, was seen on January 31, 1944. She had had regular periods until 3 months before. Since then she had had occasional bleeding. On examination the cervix

bled easily from the posterior lip but there was no evidence of tumor. A vaginal smear was positive for cancer. No biopsy was done. At operation for endometriosis on March 3, 1944, the cervix was found exposed and red. A total hysterectomy was done. The pathologist's report follows: "Along the posterior lip at the junction of the portio with the endocervix the mucosa is bluish gray and granular over an area measuring 1 cm. across. Diagnosis: epidermoid carcinoma *in situ* of the cervix."

E.P., M.G.H. No. 335303, aged 70 years, quadripara was seen in December, 1941 because of a pyometrium. This was drained and the patient was well until April, 1944, when she returned with symptoms of recurrent pyometrium. A vaginal smear was positive. Dilatation and curettage were performed, but no tissue could be obtained because of the extensive pyometrium. Hysterectomy was performed. The pathological diagnosis was adenocarcinoma of the endometrium.

A.M., M.G.H. No. 250798, aged 50 years, secundipara was seen because of vaginal spotting for 6 weeks. A cervical polyp was noted on vaginal examination, but no tumor of the cervix was visualized. Vaginal smear was positive for cancer. A biopsy was done. The pathological diagnosis was epidermoid carcinoma, grade III. A Wertheim operation was performed. The lesion was found to be in the endocervix and to measure 1 centimeter in diameter.

These cases illustrate that the vaginal smear is of great value in the discovery of unsuspected cancer. In 5 of the cases the cancer was not recognized although it was in that portion of the cervix which could be easily visualized. In 2 (the carcinomas *in situ*) the biopsies did not establish a diagnosis. The case in which both pyometrium and carcinoma of the endometrium were present is an excellent example of the aid the vaginal smear may render in establishing a diagnosis of cancer.

The case with carcinoma of the endocervix presents a special problem. If a woman has an early, symptomless tumor in that region mere vaginal examination of the cervix will not rule out the presence of carcinoma. This is true, of course, also in the endometrial carcinomas. By the time symptoms appear the tumor may have advanced to a stage where it is incurable. A vaginal smear may disclose the presence of such tumors in an early stage.

DISCUSSION

For the diagnosis of uterine cancer inspection and palpation have been found to have obvious limitations. For this reason various aids to earlier diagnosis have been suggested. In 1931 Schiller advocated painting the cervix with a solution of iodine. The normal tissue of the cervix stains dark brown because of the glycogen content of the cells. Because of the lack of glycogen in leucoplakia and cancer, the cells stain very lightly or not at all. Unfortunately erosions and inflammation also take the stain to a very limited degree so the picture may be confusing. The greatest value of the Schiller test is that it indicates those portions of the cervix from which the biopsy should be taken.

Another method proposed for early diagnosis is the colposcope developed by Hinselmann. The colposcope has been found to be of little practical value in examining large numbers of women, not because of any error inherent in the method but because of the gynecologists' unfamiliarity with the magnified cervix.

The most important method is the biopsy. It establishes the diagnosis. However, the biopsy is not infallible. It must be taken in that portion of the cervix where tumor is present. If the tumor is clearly visible the site of the biopsy may be easily determined. The chances of missing the tumor if the cervix merely presents a suspicious appearance are greater. Two of our cases of carcinoma of the cervix *in situ* were not demonstrated by biopsy, though one was reported as "? carcinoma *in situ*" and the subsequent negative biopsy was taken as near the same site as possible. Davis reports that in a study of 1200 cervical biopsies 258 sections showed no squamous epithelium and 300 were without gland tissue. It is evident that even assuming the most accurate histological diagnosis the efficiency of the biopsy in this group was only 75 per cent. It is perhaps important to note that in our 1559 smears[1] only 14 smears were unsatisfactory for purposes of diagnosis. Biopsy, moreover, requires certain operative facilities and it is not practical to carry it out on a large series of patients not suspected of cancer. A method which can be accomplished more easily and is still accurate would be a

[1]If our statistics are considered from the standpoint of individual vaginal smears rather than cases no significant difference appears. There were a total of 1559 smears and 62 mistakes in diagnosis. This makes the total error 4.0 per cent, which is identical with the error by case. The error on the negative side—that is the "false negatives"— is 9.3 per cent. The error on the positive side—that is the "false positives" —represents a 2.8 per cent error.

great aid in early diagnosis. We believe that the vaginal smear represents such a method. We certainly do not feel that it should replace biopsy but rather that it is a very valuable adjunct to biopsy. Its advantages are: It can be carried out on a much larger group of women, due to the ease with which a specimen may be obtained. It does not require special facilities. Any doctor in his office may take a vaginal smear and send it to a central laboratory where it can be examined by technicians trained in the method. The region examined is not limited by the size of the sample taken: the smear takes a fair sample of all cells desquamated into the vaginal secretion. It is not an expensive method.

The vaginal smear has the disadvantage that it does not show the grade of malignancy; moreover in some instances it is impossible to say from the study of the cells desquamated into the secretion whether the cancer is cervical or endometrial.

CONCLUSIONS

1. The vaginal smear technique is an accurate method of diagnosis of cancer of the uterus.

2. Vaginal smear and biopsy are complementary techniques which used together will enhance the effectiveness of the diagnostic clinic.

3. The most important contribution of the vaginal smear technique may be in cancer control. Large numbers of women may be screened and those with positive smears studied further by biopsy.

4. We do not regard a negative smear as excluding cancer; nor do we regard a positive smear, without biopsy corroboration, as an indication for surgery.

SUMMARY

We have presented 1015 cases studied by vaginal smear, with a diagnostic error of 4.0 per cent. Difficulties in diagnosis are discussed. The accuracy of the method is emphasized. Mistakes are evaluated. Eight early cases of uterine cancer demonstrated primary by vaginal smear are discussed. The value of the method for cancer control is suggested.

Our statistics have been reviewed by Dr. Herbert Lombard of the Massachusetts Department of Public Health.

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THE OPERATIVE TECHNIQUE OF COMPLICATED VESICO-VAGINAL AND URETHROVESICOVAGINAL FISTULAS

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THERE is a general impression, fostered by the reiterated statements of textbooks, that to cure a vesicovaginal fistula requires a superlative degree of skill and a large number of special instruments. It is true that quite a number of fistulas we see have been operated upon by others. Masson and Wilson, 1941, report: "29 out of 48 cases had 90 operations, or more than 3 per patient." Even so it must be realized that to attain a high degree of skill at any operation requires practice, and, as vesicovaginal fistulas are not common, it is not possible for the average operator to obtain the necessary practice and knowledge of the various types of complications. The literature, though extensive, is not sufficiently detailed. This article, summarizing 16 years' experience, is written with the object of assisting the "intermittent" operator, as our opinion is, that provided the operator has a good theoretical knowledge of the various technical details and complications, he will obtain good results.

With this object in view, 3 types of complicated fistulas have been illustrated to indicate the details of technique, i.e., (1) lateral type (Figs. 1, 2, 3, and 4). Adherent to the descending ramus of the pubis (and usually associated with partial destruction of the urethra); (2) type with the upper portion of the urethra involved and which requires reconstruction; (3) large fistulas.

All operations have been by the vaginal route (flap splitting type) first described by Collis (1861), later by Lawson Tate (1889) and extended by Mackenrodt (1894). Reference is invited to the detailed review of the literature and bibliography by Naguib Pacha Mahfouz (1938). To him and to all other writers on the subject we offer our acknowledgments and appreciation.

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TYPES OF FISTULAS AND PRELIMINARY STUDY

A careful preliminary study of the fistula is essential. Simple fistulas involving the bladder and free from, or with, slight fibrosis, are easily cured by adopting the principles to be described. Complicated fistulas present greater difficulties owing to their varied nature as a result of destruction of tissue and resulting fibrosis. Rarely are two the same. Any or all of the following complications may be present:

Stenosis of the vagina in all degrees, the most severe being when the normal vaginal walls are replaced by rigid fibrous tissue and the orifice admits one finger, or, partial stenosis the result of patchy fibrosis may be present.

Fibrous bands. The commonest type is a transverse band at the junction of the upper and middle thirds of the vagina causing an hour glass contraction, in the upper portion of which is the cervix and often the obscured fistula. The consistency of the band is frequently of cartilaginous consistency.

The size of the fistula varies from pinpoint to the whole vault of the vagina in which case the bladder is prolapsed. The *shape* varies considerably and is governed by the site and amount of fibrous tissue, e.g., a common type is a transverse oval, one or both ends being fixed by fibrous tissue to the rami of the pubes. The *position* of a fistula is not constant. It may be central and easily accessible, or high up behind the symphysis. A common and difficult site is high and disappearing from sight laterally and behind the descending ramus of the pubis, to which it is adherent.

Mobility of the cervix is often impaired and in some cases the cervix is completely immobilized by a solid mass of fibrous tissue thus considerably increasing the difficulties of obtaining a good exposure. The fistula may be completely immobilized and attached to one or both descending rami of the pubis, or to the posterior surface of the symphysis, or, it may be in the center of a mass of fibrous tissue.

Fig. 1.

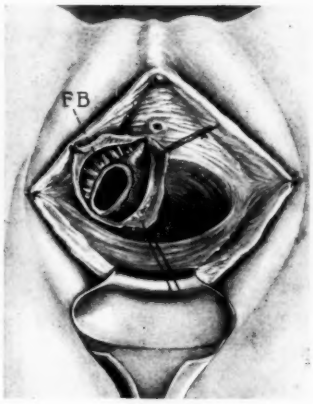


Fig. 2.

Fig. 3.

Fig. 1. Lateral fistula adherent to the right descending ramus, upper portion of urethra destroyed. Dotted lines indicate incision.

Fig. 2. Vaginal mucous membrane flaps have been separated and are held in retracted position by sutures. Fibrous bands, *FB*, seen attaching the fistula to the descending ramus. On opposite side bands attaching fistula to cervix.

Fig. 3. All fibrous attachments have been cut or broken down with the finger. The fistula, urethra, and bladder are freely mobilized.

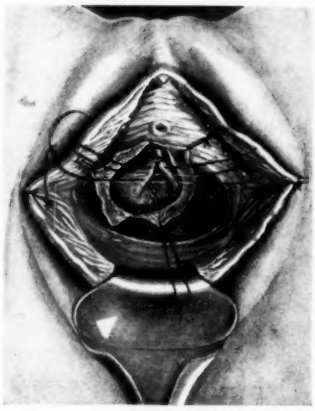


Fig. 4.

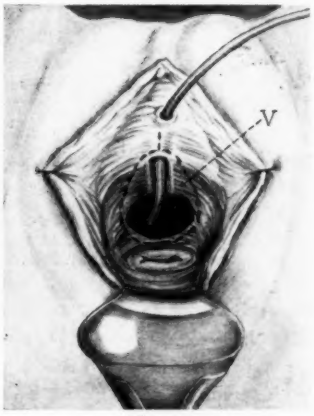


Fig. 5.

Fig. 4. The fistula has been closed by two vertical Lembert sutures which have included the urethra. Plication sutures are shown in the urethra and bladder. Note the mobility. The rubber catheter is omitted.

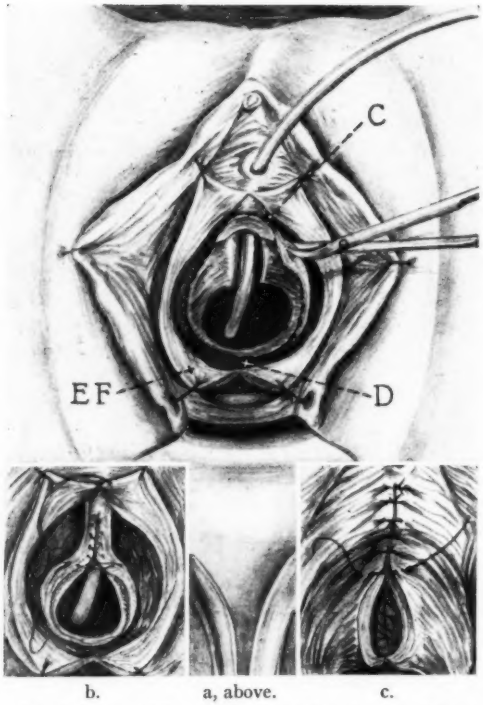
Fig. 5. Fistula with extensive destruction of the urethra. The tissues at the side of the catheter will be used to form the lateral walls and roof of the reconstructed urethra. *V*, Vaginal mucous membrane.

Finally, the urethra may have been destroyed in part, or, rarer (2 cases) in its entirety. In an average complicated fistula, half the urethra is absent, to be considered later. The upper urethra may be occluded by fibrosis.

Careful preoperative study of these many points will be well repaid, and during this study a plan of operation should be prepared. If necessary, the patient should be anesthetized.

ONE OR TWO STAGE OPERATION

The large majority of fistulas can be cured by one operation (of 85 operations, 78 were one stage). With large fistulas, a two stage



b. a, above. c.

Fig. 6. Mucosal flaps, *EF*, reflected and sutured laterally. At the top is the mobilized urethra. The scissors are seen beginning to undercut the tissue which is to be made into the new urethra. Note their position. The dots in upper half indicate the edge of the tissue. b, The first vertical Lembert's suture. c, Suture of vaginal mucosa.

operation, based on reducing the size of the fistula, is worth considering, e.g., Case 592/42.

Patient, a quadripara, had a urethrovaginal fistula which admitted three fingers; three-fourths inch of urethra remained. On June 8, 1942, the fistula in the bladder *only* was mobilized and closed over a No. 4 rubber catheter. On July 13, 1942, the fistula admitted one finger. The urethra was mobilized completely except for ¼ inch at tip. The fistula was mobilized, but mobilization was only fair, and one suture was possible. A catheter was used for 23 days. Result, cured.

We are very favorably impressed with deliberate two stage operations for large fistulas. As the urethra is usually partially absent, care should be taken to confine the first operation entirely to the reduction in size of the bladder fistula and thus reduce the formation of fibrous tissue in the urethral area.

PREOPERATIVE TREATMENT AND PREPARATION OF THE PATIENT

Cystitis is treated by irrigating the bladder and vagina twice daily with normal saline of a temperature not higher than 100 degrees F. If hotter than this a local hyperemia is produced which increases oozing at operation. Excoriations of the vulva and thighs are treated by sitz baths followed by an ointment of equal parts of zinc oxide and lanoline. A mild aperient is given the night before and an enema on the day of operation. The operation area is shaved in the ward and prepared on the operation table by thorough washing with either ether soap, or soap and water—the area being irrigated at the same time with sterile water. The area is then dried with cotton wool and painted lightly with tincture of iodine or other antiseptic. We have abandoned the use of drugs said to be urinary antiseptics.

THE OPERATION

Instruments. The special instruments used consist of: (1) Irwin Moore's cleft palate scissors—curved on the flat. The cutting edges being 1¼ inches long and the points specially ground to a long bevel; (2) long tonsil dissecting forceps—one pair with and one without teeth; (3) angular nasal forceps (Luc's) for swabbing; (4) Mayo's round bodied needles No. 18 with No. 0000 or No. 00 catgut for closing the fistula, and No. 12 with No. 1 catgut for the vaginal mucosa; (5) Bozeman's needle holder; (6) a sharp pointed cataract or any small sharp pointed knife; (7) a standard set of gynecological instruments.

We have found no use for the large variety of special scissors, knives, etc., devised for fistula work; the simple instruments here described have sufficed for all purposes. Retractors (except perineal) are rarely used as they obscure the vision.

Position of the patient during operation and exposure of fistula. The correct sitting of the patient and operator in order to provide the maximum exposure is of first importance and requires care. Shoulder rests are fixed to the table and the patient is placed in the lithotomy position. The operator sits as low as possible on an adjustable stool. The table is now raised and tilted, and the buttocks are raised to a

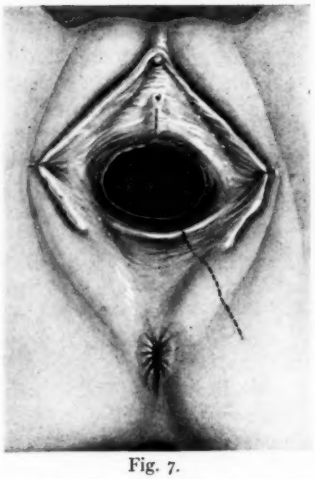


Fig. 7.

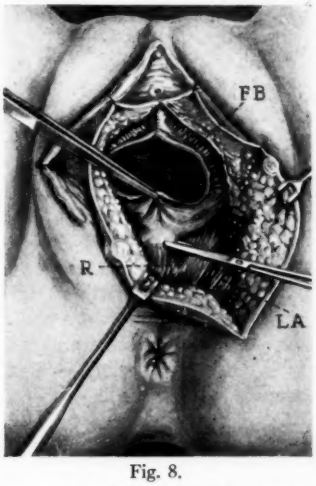


Fig. 8.

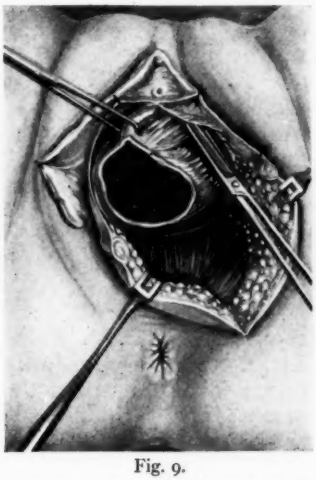


Fig. 9.

Fig. 7. Schuchardt's incision (should be more lateral) for 2 finger fistula.

Fig. 8. The incision has been deepened to the levator ani which can be cut if necessary. Fibrous bands can be seen, *FB*. The fistula is being separated from the rectum, *R*, *L A*, levator ani.

Fig. 9. Fibrous bands should be cut as near the bladder as possible and not as illustrated. Note the free mobility.

height and inclination that provide the best possible exposure of the fistula. The resultant position is usually with the patient at 15 degrees and the vulva at about eye level. Adjustments are made as required during the operation. A good head light is essential. The labia minora are retracted laterally by suturing them to the inner portion of the thighs, the sterile sheet being included in the sutures.

In the majority of complicated cases it will be necessary to provide for additional exposure by means of Schuchardt's incision which can be made on the left or right, but more commonly on the left side. The left forefinger is inserted into the vagina and the posterior wall is depressed toward the anus. This safeguards the anal canal and stretches the labium. Cutting laterally, the operator makes an incision in the left labium at the junction of the middle and lower thirds. This incision is continued upward, through the vaginal mucosa and on the posterolateral wall (still cutting outward) as high as is necessary. Externally it is carried downward in a curve with the convexity outward, to a point midway between the tuber ischii and the anus. The incision can be deepened as much as is required, and, if necessary, the levator ani divided. By means of this incision the vagina can be turned into the shape of a wide funnel with the fistula at the top and excellent exposure is obtained. Double incisions (right and left) are rarely needed. A modification of the incision (Hayes, 1937) has been described, which enables skin flaps to be fashioned and turned into the vagina for the treatment of stenosis of the vagina.

Figures 7, 8, and 9 illustrate Schuchardt's incision (the beginning of which is too medial) used to overcome stenosis caused by a transverse fibrous ridge in the vagina, and indicates the exposure obtained.

Hemorrhage during operation is usually considerable. Infiltration of the operation area with adrenalin 5 minims to 1 ounce reduces the amount of oozing. No attempt at hemostasis by means of forceps and ligature is made. Any visible bleeding point is controlled by underpinning with needle and catgut. Oozing and moderate bleeding are disregarded. The first assistant constantly places gauze swabs of suitable size in the vagina, which the operator uses and discards. Time should not be wasted in endeavoring to check any bleeding which does not come from a spurting vessel.

The principles and steps of operation. In order to clarify the technique described, illustrations of 3 types of complicated fistulas, drawn from sketches made during operations, are shown. It should be noted that even with perfect exposure fistulas are not so near the surface as the artist, for technical reasons, depicts. They should be visualized as being *inside*, and not *outside*, the vagina, so much so that in some cases the operator is working very high up at the "ends of his instruments" and by touch.

1. *Incision of vaginal mucous membrane and exposure of the fistula or urethra or both* (Figs. 1, 5, 7, dotted lines). It will be noted that the edges of the fistula are not pared, as if so the bladder is liable to retract and postoperative hemorrhage may result. In 2 cases excision of the edge of the fistula resulted in postoperative hemorrhage, and the bladder was completely filled with blood clot. With the present technique, no such complication has occurred. The first cut around the fistula is made about $\frac{1}{16}$ inch from the edge with the object of marking out the incision. Joining this an incision over the urethra and one toward the cervix are then made. The incision is deepened to the connective tissue plane over the bladder and urethra, by holding the vaginal mucous membrane with toothed forceps and cutting with the curved scissors. When the connective tissue plane has been entered, the fistula edge is held posteriorly, the lower blade of the scissors is slipped in, and, by cutting anteriorly on both sides in the incision line, the vaginal mucosa on both sides is separated up to the incision over the urethra. The vaginal mucosa is next separated from the urethra by cutting with scissors and blunt dissection. The resulting right and left flaps are now freed widely by holding the flaps with toothed forceps and by scissor dissection. The flaps are then adjusted and sutured to the labia minora, well out of the way, and in a position that will give the best exposure of underlying structures. This provides for permanent retraction. It is advantageous to make the incisions as long as possible.

2. *Mobilization.* As sutures under tension will cause edema and eventually cut through, free mobilization of the part to be sutured must always be the object in view. Figures 3 and 9 viewed by holding them at eye level and at an angle of 45 degrees indicate what is meant by free mobilization. In both these cases there were dense adhesions holding the fistulas immobile. After mobilization any portion of the fistulas could be freely moved in any direction. The edges were easily approximated and suture could be performed without tension. The ideal to aim for is to be able to seize any portion of the fistula with forceps and pull it in any direction with absolute or moderate freedom. While this ideal may not in every case be attained, it should always be aimed for.

Immobilization is produced by fibrosis which, as stated, may vary from simple fibrous bands to sheets of fibrous tissue of cartilaginous hardness. Whatever the type and degree of fibrosis present, free mobilization can be secured only by cutting through any obstructions with the curved scissors or breaking them down with the first finger.

Before adhesions are cut or broken down, it is important to orient the position of the bladder by means of a curved probe or the first finger. This will obviate a traumatic perforation particularly when operating on large fistulas.

Fibrous bands and tissue (Figs. 2, *FB*, and 8, *FB*) are palpated by the first finger and then cut. It will often be found that, after cutting the superficial adhesions, deeper and denser bands firmly uniting the fistula to the descending ramus and symphysis remain. Very often they can be freed from the bone by using the index finger, or by palpating with the tips of the scissors and then cutting. Although we prefer palpation and cutting with the scissors, if free mobility does not result, we have no hesitation in utilizing the first finger with considerable force to break down any connections between the bladder, urethra, and the posterior surface of the symphysis pubis and descending rami. Figures 8 and 9 illustrate fibrous bands *in situ* and being cut to provide the necessary mobility.

When the urethra is destroyed special treatment is required in regard to mobilization, and, in dealing with these cases, it is advisable to consider: (1) The urethra is a tube for the

conduction of urine from the bladder. Large portions of it can be destroyed, but if the remainder can be joined to the bladder perfect function results, even if the normal length of the urethra is *not* restored. (2) Providing one-third inch of urethra is available, satisfactory reconstruction can be effected. When the upper portion of the urethra is destroyed the remaining portion contracts. After it is completely mobilized it can be elongated to approximately double its length. Even a small fragment of urethra is of value and can be utilized. (3) A successful result will depend on: (a) careful planning of the incision, (b) special mobilization, and (c) suturing.

The description of an actual case will clarify the various points.

CASE 77/37. Patient was a septipara having had 6 normal and the 7th an abnormal delivery with baby born dead, followed by incontinence. Contracted outlet T..... at o..... 2¾ inches. Operation was performed March 2, 1937, through a left Schuchardt incision. Exposure was poor on account of the narrow subpubic angle. The fistula, high and behind the symphysis, admitted the index finger. Two-thirds of the urethra was destroyed and the bladder was involved. Incision was made according to dotted lines in Figure 5. A rubber catheter had been passed through the remnants of the urethra into the bladder. The middle third was seen lying on the remaining portion of the destroyed urethra, the edges of which were clearly shown for descriptive purposes only. In practice these edges will not be seen and from the catheter to the dotted lines on both sides will be smooth tissue. Note that the incision is planned in such a manner that the smooth tissue can be sutured by a vertical suture over the catheter (Fig. 6b) thus reconstructing the urethra. The right and left external flaps were then reflected and sutured to the labia minora (Fig. 6a, *EF*). The intact portion of the urethra was then mobilized up to the external meatus by blunt scissor dissection on its lateral and posterior surfaces. The degree of mobilization of a urethra will vary with the amount of urethra remaining. It may, when the urethra is long, be necessary only to mobilize anteriorly and laterally. In this particular case complete mobilization was necessary. When this was completed the scissors could be passed from one side to the other and deep to the portion of urethra seen in Figure 6a, *C*. The next step was to undercut the area internal to the dotted lines in Figure 6a. This undercutting is necessary in order that the tissue medial to the dotted lines may be sutured over the catheter. The scissors are shown beginning to undercut. It is more convenient to begin this step higher up and as a continuation of the deep plane of the mobilized urethra. Undercutting was continued on both sides and finally deep to the tissue on which the catheter was seated. The bladder was then mobilized. The result was a freely mobilized urethra and bladder and joining the two a piece of tissue which was to form the upper portion of the urethra. A vertical Lembert's suture was then inserted commencing at *C* on the side of the urethra and including the two edges of the tissue to form the anterior and lateral portions of the reconstructed urethra, then on to the bladder wall and ending at *D*, Figure 6a. Figure 6b shows the suture passing from completed urethra on to the bladder wall. A second supporting Lembert's suture was then inserted. Plication sutures were inserted in the bladder wall (Fig. 4). These were inserted until the catheter was a tight fit. The vaginal mucosa was then closed (Fig. 6c).

3. Suturing. The object of suturing is to make a watertight joint and much depends on the care with which sutures, particularly the first, are applied. Patience and accuracy are essential, and, if the operator is not satisfied that he has the correct portion of tissue on the needle, another attempt should be made. The same accuracy should be aimed for as in an intestinal anastomosis, and, as the working space is often confined, a considerable amount of maneuvering is often required. Around a fistula is an area of fibrosis and this area, which is tough and strong, should—with as much other tissue as possible—be included in the first suture.

As the edges of a fistula are not excised, edge to edge suturing is valueless. The edges must always be inverted with the forceps before the necessary tissue is picked up with the needle.

The standard suture is placed vertically, as by this means it is easier to reduce the lumen of a dilated urethra and to plicate the bladder in the region of the new internal sphincter (Fig. 4). In irregularly shaped fistulas the sutures have to be placed in the most convenient position. It may be necessary to suture transversely or diagonally, and, on one occasion a triradiate suture was necessary. Every effort should be made to insert a second Lembert suture or to cover and reinforce the first suture line with borrowed tissue. If this cannot be done, the need for the careful insertion of the first suture is even more apparent. In high oval fistulas adherent to the rami of the pubis, it is advisable to use two sutures and, first, suture each angle, gradually

working toward the center where the sutures are tied.

LARGE FISTULAS

The size of a fistula is no criterion of its curability. In many cases a large two finger fistula is easier to cure than the small adherent type (Figs. 7, 8, and 9).

CASE 465/39. Patient suffered from incontinence following the birth of a dead baby after 3 days' labor. She had had one previous operation. Operation was performed May 19, 1939, through a Schuchardt incision. The fistula admitted 2 fingers, was high under the symphysis and extended widely to the left and right. The upper two thirds of the urethra was destroyed. Mobilization of bladder involved separation of many adhesions and fibrous bands high behind the symphysis and attached to both descending rami. The uterus and adnexa were absent. No. 0000 and No. 00 vertical Lembert's sutures were used. The bladder was plicated. To provide covering for the bladder the posterior vaginal wall was freely separated from the rectum and sutured transversely. Result, cured.

The accompanying illustrations depict clearly: (1) Schuchardt's incision and resulting excellent exposure; (2) the free mobilization resulting from thorough freeing of adhesions; (3) that large fistulas can be cured if extensive dissection is made.

The internal sphincter and large fistulas. The question will arise—How is sphincteric control resumed after operations on bladder fistulas of large size, i.e., 2 to 3 fingers, and due to the destruction of a large amount of tissue? The answer is, that provided the fistula can be closed and the area at the junction of the urethra and bladder reduced to an optimum size, sphincteric control will result. We invariably insert a No. 8 rubber catheter before or after closure of the fistula. Plication sutures in the region of the bladder-urethra area are then inserted until a fairly tight fit is obtained. If it is deemed necessary the urethra is then plicated.

CLOSURE OF THE VAGINAL MUCOSA AND PACKING

Interrupted sutures are inserted and if oozing is excessive a small piece of rubber glove is inserted for 24 hours. The vagina is then tightly packed with gauze which is removed after 8 hours.

POSTOPERATIVE TREATMENT

The careful attention to details is as important as the details of operation. There are two principles to observe, namely, (1) to keep the bladder empty, and (2) to keep the stitches clean.

Bladder. We have utilized various mechanical and water pumps for the purpose of keeping the bladder empty, and, also suprapubic drainage and nursing the patient on her face. None has been completely successful as such measures require constant and expert supervision. An indwelling catheter connected to a bottle tied to the side of the bed, or placed in a bottle between the patient's legs has given us the best results.

Stitches. The vaginal packing is removed after 8 hours and nothing more is done for 3 days—after which and once daily, a small bivalve or posterior speculum is inserted into the vagina and the stitch line is exposed—the patient being in Sims' position. The stitch line is then thoroughly syringed with normal saline, a 10 cubic centimeter syringe fitted with an intramuscular needle being used. This method enables the stitch area to be very thoroughly cleaned and is far superior to douching. The vagina is dried with cotton wool and painted with acriflavine and glycerine. Stitches which show signs of infection are removed and the remains or all stitches are removed by the 8th day.

Even when the wound breaks down, the regular and methodical cleansing described should be continued and the catheter retained for at least 21 days. A number of our wounds have broken down, but with such treatment, have eventually healed. Even if this does not happen, a clean wound has less resultant fibrosis than a dirty one, and a second operation is therefore easier.

If union is good, the catheter which is removed daily—cleansed, boiled, and replaced—for 10 to 12 days, is then removed for periods of 2 hours daily. These periods are increased daily, and, when the patient is able to retain urine during the whole day the catheter is completely removed. The stay in bed averages 21 days. The catheter is kept in the bladder during the night until daily bladder control is obtained.

WHEN TO PERFORM A SECOND OPERATION FOLLOWING FAILURE OF THE FIRST

Theoretically the tissues should be in good condition 6 weeks after the first operation. Experience and the following case notes show that contraction goes on for some considerable time after operation and small fistulas tend to heal spontaneously.

CASE 164/38. Operation was performed October 20, 1937. The urethra was ½ inch long. The fistula easily admitted 2 fingers. The ureteric orifices were visible. The remnants of the cervix were fixed. A left Schuchardt's incision was made. The entire urethra was mobilized. Extensive dissection was carried out behind the symphysis. The bladder was freely mobilized. Result, failure. Second operation was performed February 18, 1938. The fistula was 1 finger in diameter, the bladder was prolapsed. The urethra and bladder were mobilized. One suture only was possible. Result: bladder control was good, but there was a pin point fistula in the urethra. March 4, 1938, the fistula had healed spontaneously. Cured.

CASE 981/37. Operation for rectovaginal fistula had been performed October 12, 1937. On April 4, 1938, a second operation was performed. The fistula admitted 2 fingers. The ureteric orifices were visible. The urethra was ½ inch long. Remnants of the cervix were visible but the cervical canal was not found. The entire urethra was mobilized. The bladder required finger dissection behind the symphysis. Prognosis was fair as regards union but doubtful regarding sphincteric control. April 16, 1937, result: failed, fistula admits one finger. Patient was to return in 3 months but did not return until 1 year later. Operation was performed May 25, 1938. The urethra and bladder were mobilized. The one finger fistula has contracted to a pinpoint. Suture and plication of urethra and bladder were done. Cured.

These two almost identical cases serve to illustrate important points, i.e. (1) fistulas resulting from an attempt at repair, contract to remarkable degree and no object is gained by an early second operation. We fix the minimum average date for the second operation at 6 months; (2) pin point fistulas resulting from an operation invariably heal spontaneously.

ABSTRACT OF OPERATIVE RESULTS

	Total	Cured	Partially cured	Failed	Died
1937 series	33	29	1	2	1
1944 series	52	44	2	5	1
Total	85	73	3	7	2
Per cent		85.88	3.54	8.23	2.35

DETAILS OF OPERATIVE RESULTS

	Total	Urethrovesicovaginal				Vesicovaginal			Urethrovaginal		
		Cured	Partially cured	Failed	Died	Cured	Failed	Died	Cured	Failed	Died
1937 series	33	15	1	—	—	13	2	1	1	—	—
1944 series	52	32	2	2	1	5	3	—	7	—	—
Total	85	47	3	2	1	18	5	1	8	—	—

RESULTS AND PROGNOSIS

Of 33 cases previously reported (Hayes, 1937) 6 only were of simple type. In the 1944 series, 2 only were simple. The availability of such a large percentage of complicated cases is undoubtedly due to the fact that the large proportion of simple fistulas are easily cured and the failures drift into the larger hospitals. Two patients died: Case 1039/39, of uremia on the 4th day; Case 31/36 of blackwater fever following a very easy operation on a ½ inch fistula. In the former patient the fistula was large and the operation difficult. The ureteric orifices were obviously compressed by the sutures and the latter should have been freed on the 2d day. In 5 cases rectovaginal fistulas were present and were operated on prior to the vesicovaginal fistula. In 2 cases the urethra was entirely absent. Three patients presented the unusual feature of complete absence of the uterus and adnexa—proved by intraperitoneal palpation. They all had had long labors and the conclusion is that due to compression and gangrene, extrusion of the uterus and adnexa occurred. Eight patients required two operations. Seventy-three of 85 patients were cured. The results in 3 cases are described as partial cures, having pinpoint or probe fistulas remaining on discharge, and patients were advised to return if not cured. Invariably this type will heal spontaneously, and as the patients did not return, it is reasonable to presume that they healed. If these cases are added to those cured a percentage cure rate of 89.85 per cent is obtained, which, considering the variety and complications encountered, is adequate proof that the flap splitting operation is a satisfactory operative method.

It is interesting to note that we are unable to prognose accurately the result of an operation. Repeatedly we have recorded "prog-

nosis bad" and the result has been a perfect cure and *vice versa*.

CASE 126/44. Cicatrization of vagina which admitted one finger. The urethra was ½ inch long. A one finger urethrovaginal fistula was adherent to both rami of the pubis. Mobilization was difficult and not complete. One suture only was possible. Prognosis was bad. Result, cured.

This experience has been fairly common, and we now do not assess operability by examination, but invariably make one or more attempts at closure.

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SAPHENOFEMORAL LIGATION WITH THE IMMEDIATE RETROGRADE INJECTION

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THE purpose of this paper is to discuss the treatment of varicose veins of the lower extremities by means of preliminary ligation of the offending veins together with either the immediate or subsequent injections of the sclerosing solution.

The discussion is based on an experience gained while doing and caring for 2,582 ligations in 1,952 patients. Of this total number 633 were bilateral ligations. There were 89 cases in which the short or lesser saphenous was ligated. Females predominated 3 to 1: 1,904 females to 678 males. This preponderance of females is explained by the fact that many women come for treatment for cosmetic reasons only, while most men come only when the pain and ache in the leg is severe, or when a definite thrombophlebitis has developed. When the varicosed condition involves only one leg it shows no predilection for either—right 1,307; left 1,275.

As to age groups, we found the largest number of cases in the decade between 50 to 60 years, 33 per cent; with the next in the 40 to 50 year group, 30.6 per cent; 13 patients were under 20 years, 7 per cent; 49 patients 70 to 80 years old, 2.9 per cent; and 1 patient was 81 years old.

The normal upward venous flow is carried on by three main factors. First, the pressure of the arterial blood through the capillaries and into the veins; second, the pumping effect of the calf muscles as they contract on the deep veins, while the patient is walking; third, the suction force of respiration which causes a negative pressure in the chest during inspiration.

The theory that the preliminary ligation is the first and perhaps the most essential step in the treatment is based on the now proved fact that the flow of blood in any well developed case of varicose veins is actually reversed, that is, it is flowing downward toward the foot, instead of toward the heart, as should be the case with all venous blood. The more marked and well developed this flow has become, the more important it is that the ligation be the first step in the treatment.

The reverse flow of the blood develops because of the loss of function of the valves in the veins in the thigh and lower leg. There are usually 5 to 7 sets in the great saphenous through the thigh, with one set just outside the saphenofemoral junction, and at times one set in the deep femoral and iliac vein just above. There are several sets in the veins of the lower leg.

The loss of valve function develops for several reasons: First, and I believe foremost, a hereditary factor is present in fully 50 per cent of the cases. By this I mean the patient is born with a weaker than normal set of vein walls through some sections. Under the stress of normal life, exercise, work with its attendant straining, and the increase of intra-abdominal pressure, etc., these vein walls stretch and give way so that the vein lumen may become several times larger than normal. Thus the valves will be mere cusps on the side of the vein wall and of little value. Careful taking of histories has often shown this to be the case. The second most common cause is infections. During sickness there has actually been a bacteriemia with the infection causing damage to the valves and scattered areas of the vein wall. The weakened wall dilates under the usual venous pressure, and then more rapidly later when the valve function is lost. The third most common cause is pregnancy (10). Many have argued that the growth of the uterus mechanically causes pressure on the iliac veins and that the normal veins below just give way under this strain. This is not the usual case, for the varicose veins most often begin during the first 3 months of pregnancy, when the fundus is still small and freely movable in the pelvis. There is much evidence

to prove that there is actually a disturbance of the hormones (11) with an overdevelopment of some, such as progesterone, which permits the muscles of the vein walls to soften and stretch (10). Fourth there is the case of congenital varicose veins and the arteriovenous fistulas. These anomalies are recognized soon after birth or during the early months or years of life. They are most difficult to treat.

What varicose veins should be ligated? The patient with small varicose veins, the size of a lead pencil, with a very slight or no reverse flow can well be treated with simple injections. Any patient who does have a well developed reverse flow should be studied, and then a ligation block should be made above that point wherever it may be. Many surgeons believe that any vein large enough to be injected should be ligated first. In my opinion this is too radical, for with proper selection fine results have been obtained in many hundreds of cases over a period of years. Personally, it would seem that any vein that has been injected with care, and there has been a recurrence, should be ligated. Any great saphenous, 1 centimeter or larger in diameter at the saphenofemoral junction, or the short saphenous the same size at its junction with the popliteal vein, should be ligated. Any vein with a definite reverse flow through a perforating vein, and which does not come from the saphenofemoral junction, should be ligated where found. The possibility of the presence of compensatory, dilated veins, must always be thought of and especially so after a history of phlebitis. Compensatory veins may develop following a blockage of the deep system, but after the deep veins heal and become recanalized, and again are patent and functioning, we should study the varicosities present, and if they show the findings of typical varicose veins with a marked percussion pulse (14), P.P.T., (Fig. 1) at the groin, and a reverse flow, they should be ligated and injected just the same as any other varicosed vein in any individual.

The Trendelenburg (17) test is the one most commonly used to determine reverse flow (13). It is simple and easily done. With the patient standing the varicosed condition is studied. The percussion pulse is followed along the vein to the groin. The patient then lies down and the leg is elevated to empty the varicosities. Pressure is then made over the saphenofemoral junction to block any outward flow. The patient then stands. If there is a marked reverse flow from the groin when the pressure is suddenly released, the empty varicosities will fill rapidly and the test is positive.

If the varicosities fill slowly with the normal accumulation of blood from the distal areas, but fill more rapidly when the pressure at the groin is released, then the test is still positive. We also have the condition in which the reverse flow is outward through a perforating vein in the thigh or lower leg. In this case the veins will fill rapidly and not become more tense when the pressure above is removed. This is a negative test. Then there are cases which have some of the reverse, outward, and downward flow from both sources. This is called a Trendelenburg double test.

The Perthe test is the one most commonly used to locate a reverse flow through a perforating vein in the lower thigh. It is made by applying a rubber tube tourniquet about the leg, and having the patient walk rapidly for 50 to 100 steps. The normal pumping effect of the calf muscles with each step will suck the blood inward from the varicosities, and thus the varicosed segments above the tourniquet will remain filled while those below will be emptied. If the test is positive, the empty veins will quickly fill from above as the tourniquet is removed. The multiple tourniquet test of Oschner and Mahorner (9) is merely the reapplication of the Perthe test at different levels, until the offending vein or veins are located. Gerald H. Pratt uses two bandages about the leg to locate the perforating veins. They work well. One bandage is applied very tightly from the foot to the groin. When the patient stands it is removed from the top down. A second bandage is then applied from the groin downward leaving about 4 inches between the bandages. In this way the perforating veins can be seen as they appear. If the test is negative and the large varicosities are compensatory veins, then the veins below the tourniquet will enlarge as the patient walks rapidly, and the patient will complain of pain in those areas and the lower leg.

The bandage test is the final proof as to whether the enlarged veins are varicosed or compensatory. It should be used on all cases that are not clear with the other tests. Here a firm, 4 inch bandage (the Ace No. 1 *four inches* wide has been found to be most satisfactory) is applied about the lower leg from the knee down to the toes going twice about the ankle and foot in a figure of eight. The patient is then told to walk four to five blocks very fast. If the patient should develop a pain in the lower leg, and in particular if this should increase, then he may remove the bandage, but if the pain does not increase as the minutes go by, then he should walk three blocks, rest, walk four blocks, rest, walk five blocks, and then report back to the office for examination with the bandage still applied. If the pain should get better, then he is to leave it on until bedtime, when it can be removed if uncomfortable. If the varicosities are compensatory the patient will have severe pains through the lower leg and foot when walking, but if they are typical varicose veins with a stagnant and reverse flow, the patient will feel better the faster he walks, and when he returns after a fast ten block walk his toes will be pink, the edematous leg will be much softer, and the patient will admit that the leg feels better than it has for a long time. Many doctors do not grasp the mechanics of the compression bandage, and the pumping effect of the calf muscles on walking. Many patients have actually been told "never to wear a tight bandage on that leg." It is a common thing for a doctor to let the patient dominate the situation, and when the patient says "I do not like the bandage, etc." he is permitted to go without the support even though the lower leg may be edematous and badly swollen. When the patient has had this kind of treatment in the past, I admit that it is a case of salesmanship to persuade him even to try wearing a bandage on the lower leg long enough to make a good test, let alone for treatment of an inflamed edematous leg with ulcerations. Again, the doctor must decide whether there is evidence that the patient has *pain* or whether it is a case of *fear* on the part of the patient, and lack of confidence in the present attending physician.

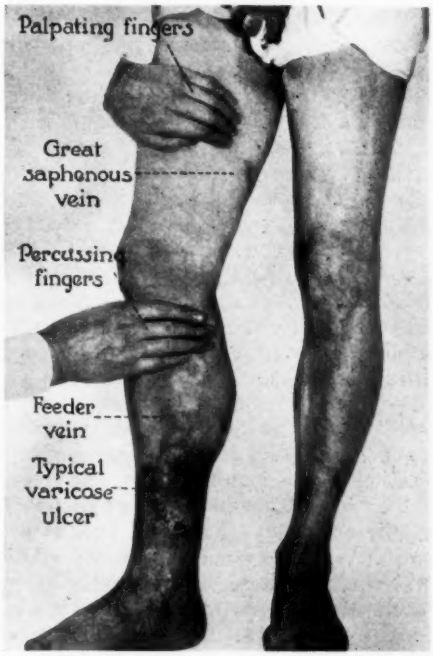

Fig. 1 Demonstrating the percussion pulse transmitted, or the *P. P. T.* Note the vein typically feeding the varicose ulcer. The great saphenous is not visible or palpable in the thigh except at the point marked. The percussion impulse made by the fingers at the knee is transmitted upward and perceived by the fingers of the palpating hand over the vein in the upper thigh. (From author's *Injection Treatment of Varicose Veins and Hemorrhoids.*)

At the time of examination we must not only settle the question of the reverse flow, and that a ligation or ligations should be done, but we must not forget the patient himself. How often we see a patient die of shock from a burn, while the doctor is meticulously caring for the burned area itself in order to avoid a later infection if the patient lives. So here we must always be on the lookout for a complicating diabetes, for a cardiorenal condition, and for the presence of a very toxic thyroid, with the varicose veins by far a secondary factor.

The diabetic patient stands surgery poorly until he is insulinized; the decompensated heart patient should be digitalized, and then he will gain much relief from the care of the varicose veins. The worry and pain of bilateral ligation with an excessive reaction may

overtax the thyroid, and a history of repeated attacks of allergy to many foods, etc. should put the doctor on his guard. High blood pressure is not a contraindication. I have often seen the blood pressure drop considerably following the treatment of the varicosed condition. Age by itself should not deter the surgeon. The patient at 80 and in good general health should be treated by a ligation if necessary, while the one at 30 should be denied treatment if he is bed fast and cannot be up and about so as to avoid a thrombus extension and embolus formation, so commonly associated with the venous stagnation which occurs with bed rest (6).

The first known efforts at treatment of this condition was by burning with the red hot iron and hot oils (1). In later years, the injections of various solutions into the vein held sway, but because of fatalities from emboli, etc., this treatment had a hectic course. With the refinement of the solutions and techniques used it became a very safe procedure. Even so it was unsuccessful in a large percentage of cases. Even as late as 1928 I had the self assurance that I could very well treat *any* case of varicose veins by the injection method alone. Because of the large number of failures in the treatment, many surgeons were looking for a more perfect method.

To Trendelenburg belongs the lion's share of the credit for the development of the theory of the reverse flow of blood in the varicose veins, but it was John Homans (4), of Boston, who was the first to insist that if the reverse flow developed from the saphenofemoral junction the correction of the condition should most properly be initiated by a ligation at that point, and above all the collateral veins. All our efforts since have merely been toward a refinement of this idea. Thus, by adding the modern ligation to the injection treatment as refined during the past 90 years, we now have the *combined saphenofemoral ligation with the immediate retrograde injections of the sclerosing solution* as the treatment of choice.

I cannot emphasize too much the importance of individualizing the patient. Study the case at hand, and treat that individual patient. What is his threshold of pain? Is it high, or low? How much can be done and yet keep the patient ambulatory? How difficult will it be to inject the varicose veins below the ligation and through the thigh? This *must* be done or there will be a high rate of recurrence. Not all patients needing ligation of the great saphenous in both legs should have them both ligated at the same time, even though as a rule this can be done. In one case endeavor should be made to spread the solution through the entire saphenous group to the lower leg, while in another, attempt should be made to limit reaction to 6 to 8 inches of the upper end of the saphenous vein.

Study of the case and decisions as to procedure are best made at the time of the initial examination. Not only is a complete record made of the distribution of the varices and other findings, but a note is made of the amount of solution to use and the extent of reaction desired in that particular case. This information is for use at the time of the ligation.

A true saphenofemoral ligation above all branches is strictly an operating room procedure. A ligation of a superficial branch in the midthigh just under the skin is something different. This procedure, unfortunately, is what is so commonly done and called a *high ligation*. To attempt a true saphenofemoral ligation in the doctors' office (2) without good operating room equipment, either means ignorance on the part of the surgeon as to what he is attempting, or a high disregard of a perfect end-result and the possibility of sudden hemorrhage and complications that will tax the ability of the best surgeon (2). An attempt to do this operation in the office is almost a criminal procedure, and one should hesitate to take the witness stand in the defense of a colleague who had done so.

OPERATIVE PROCEDURE

A wide field of operation is prepared as for a femoral herniotomy, either single or bilateral, as desired. With the patient standing on a foot stool the percussion pulse, *P.P.T.*, (14) is followed as it is transmitted upward along the great saphenous vein to the groin. A vertical mark is made over the vein at that point, and then another mark is made parallel to and one-half inch below the inguinal ligament. This

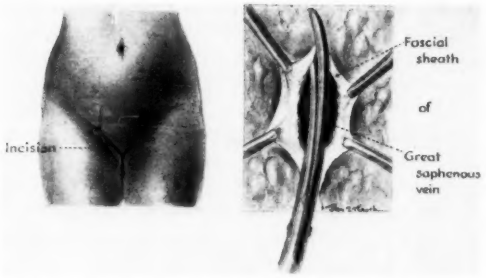

Fig. 2 a, left, Vertical marking along the great saphenous vein at groin. Transverse mark shows line of incision one finger breadth below the inquinal fold. b, Incision through the fascial sheath covering the great saphenous vein.

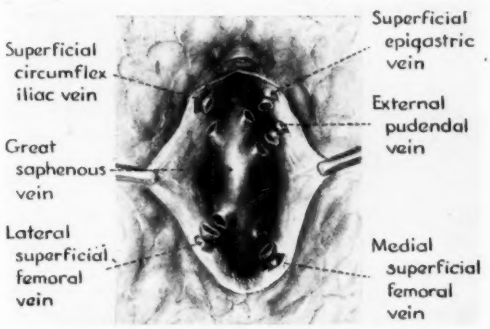

Fig. 3. Fascial sheath has been opened and stripped off. The vein and all branches have been ligated separately. The great saphenous vein is now ready to be clamped and sectioned.

mark is best made by a simple scratch with the back of the tip of a scalpel. If you warn the patient of it, and do not press hard, he will mind it but little. Additional marks are made lower in the thigh or lower leg if other ligations are to be done there.

Preferably the leg should be draped separately so that it may be raised high from the table without contamination. If bilateral ligation is being done, both legs are so draped. One per cent novocain is infiltrated through the area, care being used to carry it widely enough to give good anesthesia.

After the skin and superficial fascia have been incised, a secondary infiltration is made of the deeper layers. As the dissection is carried downward and about the saphenous vein, injection should be made also into the posterior sheath of the vein as soon as possible, as the sheath carries nerves and the patient otherwise will complain. Two or 3 cubic centimeters of novocain is then injected about the vein just at the foramen. If care as to the injection is used, the ligation can be done with little or no pain, and with much surprise and pleasure on the part of the patient. As a rule about 90 cubic centimeters of novocain is used for each side.

The incision should be adequate, about 3 inches; longer in the obese individual. As Judd (7) so aptly said: "incisions heal from side to side, and not end to end." A short incision predisposes to incomplete work and makes the chances for technical complications far greater. It is these avoidable complications that cause calamities in this work, and we should try to prevent them.

Dissection carried out directly down and under the preoperative scratch mark, will reveal the vein. The vein can also be located just internal to the pulsations of the femoral artery, or in the soft triangle between the heads of the sartorius and the adductor longus muscles. It is very simple to open the sheath and to peel it off the vein. The peeling process should be done from inside the sheath and more novocain should be injected as the sheath is peeled off (Fig. 2 and 3).

As a rule the vein is found about 2 inches below the saphenofemoral junction. During the dissection stage it is important not to use forceps with teeth as so often the vein wall is thin and is easily torn. The vein is lifted up and a curved Mixter cystic duct clamp is slipped under it. A clamp is then placed on the vein distally and the curved clamp proximally. The vein is sectioned, a stump one-half to three-quarters inch being left on the distal end. This stump will facilitate the injections later.

The fat is retracted upward, and the proximal stump is followed to the wall of the femoral vein. All branches are carefully ligated. This is very important and the dissection must be carried upward and into the foramen, so that the femoral vein can be seen both above and below. Often times branches come off directly at the foramen (3, 12) (Fig. 4). Usually

Fig. 4. Great saphenous sectioned with clamps on both proximal and distal ends. Note the tributary veins entering the saphenous in the foramen. Each vein separately ligated. A double ligature is about the proximal stump on the wall of the femoral vein. A purse-string ligature has been placed to reinforce the foramen as the stump is tucked in. The external pudendal artery lies below the foramen in about 90 per cent of the cases.

there are three branches in the last one-half inch of the saphenous vein. No. 40 cotton is used for these ligations. The presence of the small external pudendal artery is a good landmark as to the location of the foramen. The artery lies just below or above the saphenous vein at the level of the foramen, and often may be double, going both above and below. It should be ligated if it is in the way.

The femoral artery with its pulsation is located just external and can easily be injured with careless clamping of the artery forceps. Often when the clamp or ligature slips off the proximal vein stump, profuse hemorrhage develops. In most instances, amputation following ligation has been the direct result of this injury from clamp or forceps, with resultant thrombus formation and arterial blockage. This statement is made after autopsy in 2 cases and after careful study of case histories from attending surgeons in several other cases.

A No. 16 cotton ligature is placed about the proximal stump, full and flush with the wall of the femoral vein. A second ligature of No. 16 cotton, single, is then tied about the same stump as a double precaution against postoperative hemorrhage. I have had this experience. Some prefer to transfix the stump. That is all right. I prefer to use the two separate ligatures and leave a longer stump of vein. In this way there is no proximal stump left from which an embolus could come. A stump at least three-fourths to one inch is left distal to the ligature, thus eliminating worry about the ligature slipping off the end.

A pursestring ligature of No. 16 cotton is placed about the foramen (Fig. 5) so as to close the fat and fascia over it, and thus to reinforce a weak spot in the fascial plane over the femoral vein, the same as we would do with a femoral hernia. Most men do not bother with this step, but I think it is just good surgery to reinforce a weak spot in the deep fascia. It just lessens the possibility of a recurrence through a small branch that may be left even with real care.

The distal stump of the vein is then picked up with small forceps. A No. 16 cotton ligature is placed about the vein distal to the clamp. With the forceps on the vein stump in one hand, a cannula on a syringe containing the sclerosing solution is then slipped into the open end of the vein, the clamp is removed, and the ligature tied, all at the same time.

The patient is then tipped into a marked Trendelenburg position, and the foot and leg are raised high for about 1 minute, so as to drain all the blood from the varicosed veins through the communicating veins into the deep system. The table and patient are then quickly tilted into the *reverse* Trendelenburg position with the leg still held high. The leg is then quickly dropped to the table and two-thirds of the solution is injected. Since the varicosed veins are now empty and collapsed, the solution will drain down and spread widely through the branches to the calf, and at times to the ankle. After 1 to 1½ minutes the table is returned to about 10 degrees off the horizontal and the rest of the solution is injected. The wound is washed with normal saline to free it of any sclerosing solution that might have been spilled during the injections. It is then closed with two sutures of No. 16 cotton and the skin with dermal. Mastasol helps keep the dressing in place and furnishes a better protection.

As soon as the wound is dressed, separate strips of adhesive are applied over the large segments of varices so that as the thrombus develops during the next 24 hours it will be kept as small as possible. A large thrombus will liquefy and recanalize while a small one will organize with a good result.

Immediately following the operation, the patient must walk rapidly the equivalent of one block. He can then dress and go home, but must walk 5 minutes out of every hour until 10:00 p.m. of the day of operation. He is given some sort of sedative capsules for the moderate pain he will have and told to take them as needed, and to report to the office for a dressing 2 days later. That visit is very important for his comfort. If the reaction through the thigh is severe the thigh should be strapped with elastic adhesive for support. If severe in the lower leg, then a firm *4 inch* bandage from the knee to and about the foot will give much relief. Patient must continue to walk some every 3 to 4 hours during this time.

The sutures are removed at the end of a week, and either then or at a later date, the injections of the remaining patent varicosed segments are begun. If the reaction has been severe there is no harm to wait until it has subsided. But it is very important that the follow-up injections be continued until all the varices are firm and hard. Usually the injections are given every 1 or 2 weeks, and 3 to 6 at a time. These are of ½ to ¾ cubic centimeter of the same sclerosing solution. Immediately following each set of injections the patient must walk fast 3 to 5 blocks and then at frequent intervals all day long.

PREGNANCY AND LIGATION

The treatment of varicose veins during pregnancy except in the isolated case does not seem justifiable. At times much relief can be given by a few injections. During pregnancy the injection of the feeder vein into a large and rapidly forming burst is always indicated to relieve pain and to prevent the formation of this unsightly condition—a condition that cannot be completely cleared once it fully develops. The ligation of the varicose veins during pregnancy has been one hundred per cent failure, and is not recommended. These patients should be treated palliatively with the injections as indicated, and they should wear a firm *4 inch ace bandage* during the day and remove it at night.

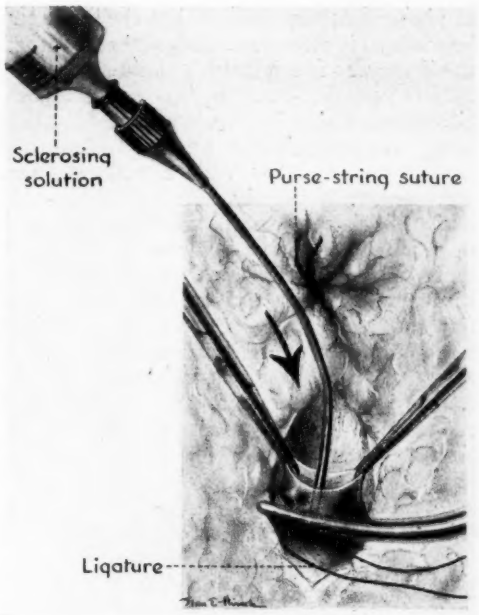

Fig. 5. Purse-string suture has been tightened closing the fascia over the foramen to reinforce the weak spot. The cannula has been introduced into the distal segment of the vein preparatory to making the injection of the sclerosing solution.

COMPLICATIONS

Complications are best divided into those of the operation itself and those of the postoperative period.

The most common and serious complication that can and may develop during the operation is a hemorrhage. Hemorrhage may come from the tearing of a large, dilated, saccular thin walled vein during the dissection; it can best be avoided by *not* using forceps or clamps with teeth. Personally, I am very careful that no such instruments are ever on the table. Another common cause of hemorrhage is the slipping of the forceps on the proximal stump during dissection, or slipping of the ligature after it has been tied. The first

can happen to any surgeon, but the latter can be avoided if the care already discussed when the ligatures are applied is exercised.

If the proximal stump does become loose, either from a poor forceps or a slipped ligature where the vein is the size of the thumb, the surgeon is faced with a real problem. The patient is usually nervous and straining. They sense that something has gone wrong, and they become more worried and tense. The blood boils up from the bottom of the wound as from a spring. Here is the potential source of calamity, and the principal reason of a good operating room. The surgeon should keep calm and quickly place a large sponge in the wound with pressure, and tip the table into a *marked* Trendelenburg position. Of course, the shoulder supports have been applied as they always should be. The leg is raised straight up and the table, patient, and leg are held in this position for 2 minutes. It is surprising to find that after that length of time the leg can be lowered to the table, the pressure removed from the wound, and there will be but little bleeding. The proximal stump is now carefully sponged and picked up and the operation continued. As soon as the stump has been reclamped the table may be leveled again.

If a postoperative hemorrhage should develop after the patient leaves the hospital, I would insist on his lying quiet while someone quickly places a clean towel over the area and maintains constant, severe pressure, until the patient can be taken by ambulance to the hospital and operating table. It should be remembered that pressure and bandage will stop any hemorrhage. The wound should be reopened and cared for as described.

CASE 1. Autopsy showed that both the femoral artery and vein had been ligated. The hemorrhage had been well stopped. Gangrene of the extremity developed with an amputation 5 days later, and exit from a large pulmonary embolus followed 24 hours later.

CASE 2. The surgeon tried to stop the hemorrhage with the patient lying in a sagging bed in a converted home hospital. He stopped the hemorrhage with the use of large Kocher forceps with teeth. After much grabbing and clamping he had a dry field, and then on careful inspection he found that he had the large Kocher forceps on the femoral artery as well as the femoral vein. It had been there, one or more times, for at least 10 minutes when he realized what he had done, but the damage was complete. The bleeding stump was again ligated and the patient put to bed. The next day the leg was cold and typically devoid of arterial supply. This patient also died of a pulmonary embolus, and at autopsy the artery was found filled with a thrombus arising from the area crushed with the heavy forceps with teeth. The femoral vein was also filled with a thrombus secondary to the trauma, and the extension upward had caused the embolus.

At times the femoral artery may lie anomalously entirely in front of the vein for 3 inches down the thigh. If the patient is very apathetic with a low blood pressure, and thinned walled arteries, with poor pulsation, as would be found in such a case, it is possible for the surgeon, not exercising proper care, to ligate an anomalous profunda femoris branch of the femoral artery. I am sure that this was what was done in one case with a resultant slough of all the area of the lower leg supplied by this branch. The patient complained of severe pain through the leg and foot as the distal injection was made under local anesthesia. The operation was completed under gas anesthesia, and the other side was ligated. The second side progressed as usual while after 2 years of hospitalization and litigation, an amputation through the lower thigh was made of the first side.

Gangrene of an extremity can happen only from a loss of the arterial supply. Gangrene could not happen as a result of the retrograde injection at the time of the ligation, as the injection is made into the returning side of the circulatory tree. The injected fluid could not get across into the arterial side by any conceivable route. It would seem that those who argue that it can, do not reason out the route and direction of the blood flow in the arterial, capillary, and venous portions of the circulation. A knowledge of the blood pressure readings found in the different areas would prove the fallacy of the idea.

The greatest source of morbidity in this series, as also with those patients seen after operation in consultation, has been the severe chemical phlebitis and the associated cellulitis following the injections of too large amounts of the sclerosing solution. By the use of the tilting technique described, by the individual-

izing of each case, and by the injections of the smallest amount of the weakest sclerosing solution that will give a sufficient reaction to produce the obliteration of the varices, this source of morbidity can be reduced to a minimum.

The excessive phlebitis and painful reaction are best cared for by bed rest, with the application of hot packs applied widely over the area for 4 hours at a time, with the patient getting up for a 5 minute walk twice daily. This regimen will cause a rapid relief of the pain, and yet prevent the stasis thrombus extension and embolus formation attendant upon steady bed rest (6). I have seen and have had cases in which the lower leg and even the entire thigh were swollen after operation. This condition, in my opinion, was due to too much solution having been injected, and to the patient not walking sufficiently to wash the sclerosing solution thoroughly from the deep veins after he left the operating room. Thus the same findings would be found as in deep phlebitis. Fortunately, I have never seen a single case in which swelling persisted after treatment of the great saphenous, and in only 3 cases after ligation and injection of the short saphenous.

Any method of treatment for a certain condition is just as good as the results obtained. Time did not permit the collection of follow-up data and statistics on my entire series of cases. However, a complete check was made on my first 1,146 cases but the information was reported on only those cases in which ligation had been done 1 year or more previously. The data would be almost exactly the same if a complete check were made today, except that there would be a definite improvement in the results.

Any discussion of the end-results and recurrences must take into consideration the pathology present in varicose veins. It is essentially one of degeneration or the result of damage and injury that may have been sustained years before. If that process and those factors, whatever they may be, are still active, more varicose veins are bound to develop as time goes by. The yearly visit to the dentist is made with the full expectation that new cavities will be found and cared for. Just so with varicose veins. We must realize that time takes its toll and that the yearly visit to the doctor will probably show new varicosities forming. Just as with the teeth, this may be a progression of the old process, not completely checked, or it may be an entirely new condition. We do know that in the average case one or two visits to the doctor a year will be sufficient to keep the varicose state well under control, and to prevent a reformation of the extensive varicosities present when the patient was first seen.

SUMMARY

This presentation is based on an experience gained in caring for 2,582 varicose vein ligations over a period of 12 years.

Every method based on sound reasoning has been tried, and conclusion has been reached that the *high saphenofemoral ligation* combined with either the immediate or subsequent injection of a sclerosing solution has given uniformly good results. For any case of varicose veins with a definite reverse flow high saphenofemoral ligation is by far and wide the method of choice.

CONVICTIONS CONFIRMED

Since this paper was prepared the privilege has been afforded me of observing the treatment of varicose veins in Boston, New York, Los Angeles, and San Francisco. The recognized leaders and outstanding men doing this work on both coasts have been visited. All this has made me realize more than ever the wide divergence of opinion on this subject and the fact that the ideal and perfect method of treating varicose veins has not yet been found. One surgeon stated that he had never done a vein ligation, and that he never would. He treated all his patients with injections only, and claimed good results although I saw several patients still needing injections months after the treatment had been started. On the other side I was more than surprised to find very good and experienced men who had practically reverted to the old vein resection and stripping operation of 20 years ago. They simply began the operation with a fine, very high saphenofemoral ligation. The stripping and resection following were the most complete and extensive I have ever seen. Sherman, in San Francisco, bases his radical stripping and resection on a most thorough course of cadaver dissection and experimental work. His efforts at seeking a basic cause of this pathologic condition must be admired. His method of combining the injections with the later radical resection is based on good reasoning, and much clinical expe-

rience. It surely does reduce the amount of venous bleeding at the time of the operation. The clinical end-results are fine, and the patients were surprisingly comfortable after operation.

After such an extensive clinical trip and having cared for and treated over fifteen thousand varicose vein patients, in whom over 3056 vein ligations have been done, I have returned to my former convictions more firmly than ever. Briefly stated they are as follows:

CONCLUSIONS

1. There are many causes of varicose veins, not all are active in the same individual.

2. Many cases are best explained by a congenital weakness or deficiency of the vein wall in scattered areas. Many have this same weakness develop following damage to the vein wall and valves by a phlebitis.

3. The hormone theory (10) as a cause of varicose veins must be more thoroughly explored and tested.

4. The presence of incompetent perforating or communicating veins as one cause of the recurrence must be accepted. The efforts of Homans (4), Pratt, Linton, Ochsner (9), Sherman, and other competent men must be recognized.

5. Finally, the great majority of cases are best explained on the basis of a degenerative condition developing in the vein wall similar to the decay of teeth, the development of gray hair, flat feet, hernia formation, hemorrhoids, etc. On this theory we can and must expect more varicose veins to form and develop as the years go by, regardless of how thorough the operative removal may have been. In my personal experience varicose veins have developed even after the best and most thorough operative procedure. But, just as the dentist will care for and repair a set of teeth, sadly neglected through the years, and then tell the patient to return every year to have new cavities filled while small, so must the surgeon treat his patients with varicose veins. He must do the best work he can for the individual case at hand by using the best method adaptable as regards the surgical phase, and combine with it some form of the injection treatment. When the result is fine then the patient is discharged with the instructions that new varicosities will probably form as the years go by, and that he should return every year to have these cared for by the mere use of a few injections while the varicose veins are small, so that the fine results obtained through much labor will be retained.

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ABSORBABLE GELATIN SPONGE AND THROMBIN FOR HEMOSTASIS IN NEUROSURGERY

Experimental and Clinical Observations

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THE introduction by Ingraham and Bailey (2, 3, 4) of fibrin foam prepared from human blood as an absorbable medium for the application of human thrombin constituted an important advance in technical neurosurgery. Recently, Correll and Wise have developed a foam-like sponge whose essential ingredient is gelatin. When dry, this sponge can be cut into sheets or pledgets of any desired thickness and dimensions, it absorbs liquids readily and its tensile strength and other physical properties make it easy to handle without fragmentation in either the dry or wet state. It has the additional advantage of being produced from a readily available substance by a simple and inexpensive process.

The use of this sponge as a hemostatic agent in neurosurgery has been carefully investigated by Light and Prentice (6) in monkeys. They found that the gelatin sponge is readily absorbable and that it has no significant toxic or irritative effects. In these respects, it was comparable to fibrin foam.

Subsequently, Light (5) employed the gelatin sponge in conjunction with bovine thrombin, in a series of human neurosurgical operations. As a hemostatic agent, the sponge proved quite satisfactory and no harmful effects of any kind were noted.

We have carried out experiments on dogs in which the efficacy of gelatin sponge has been determined and its absorption and replacement have been studied histologically. In all experiments identical observations were made upon fibrin foam, as a similar medium of already established value and safety.

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Vanderbilt University.

Concomitantly, gelatin sponge has been employed in a number of human neurosurgical operations by a group of neurosurgeons who have been kind enough to forward reports on these cases to us for analysis.

EXPERIMENTAL OBSERVATIONS

Identical procedures were carried out on all dogs with routine neurosurgical technique. Under intravenous nembutal anesthesia, the superior longitudinal sinus was exposed and two incisions about 1 millimeter in length made in it. A small pledget of fibrin foam saturated with human thrombin solution was placed upon one bleeding point, covered with moist cotton, suction applied for a few seconds, and the foam gently held in position for a few more seconds. The cotton was then removed and the foam left in place. Upon the second bleeding point a piece of gelatin sponge of the same size saturated with human thrombin was placed in exactly the same manner. The wound was then closed in layers with interrupted silk sutures.

In all instances, there was immediate and complete cessation of bleeding when either the foam or gelatin sponge was employed. The two materials seemed equally satisfactory in this regard. Because of its physical properties, the gelatin sponge was easier to cut into the desired size and had less tendency to crumble.

The dogs recovered promptly and none showed evidence of toxic or antigenic reaction.

The animals were sacrificed in pairs at intervals of 2 days, 4 days, 1 week, 2 weeks, 4 weeks, and 6 weeks after operation. The areas in which foam and sponge had been applied were somewhat adherent to the overlying tissues and the foam and sponge (or, in longer experiments, the fibrous tissue with which they had been replaced) were firmly adherent

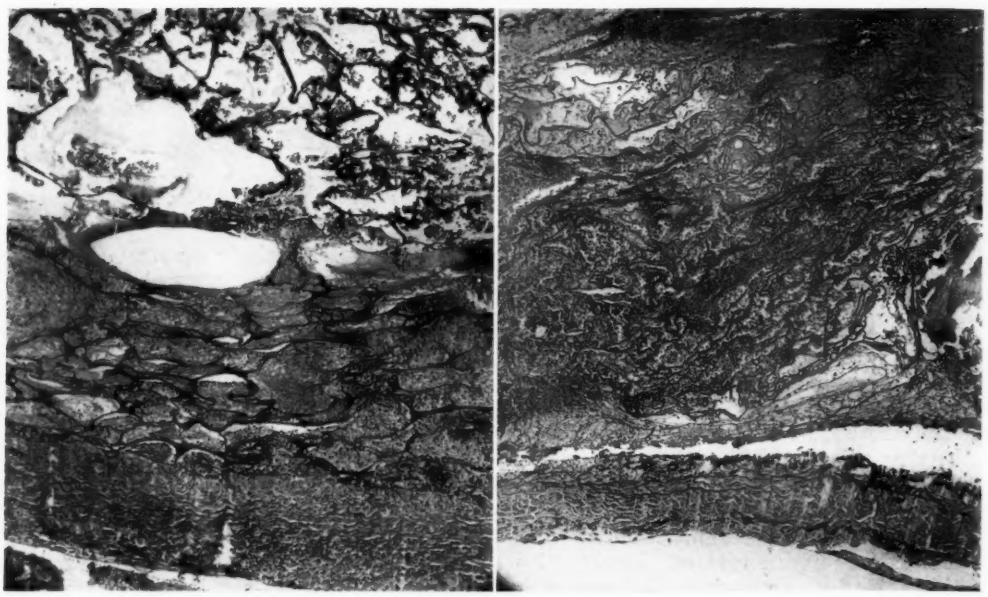

Fig. 1. Gelatin sponge, a, left, and fibrin foam, b, right, 2 days after implantation on the dura. Note the leucocytic infiltration of the fibrin filled spaces. Hematoxylin and eosin. ×70.

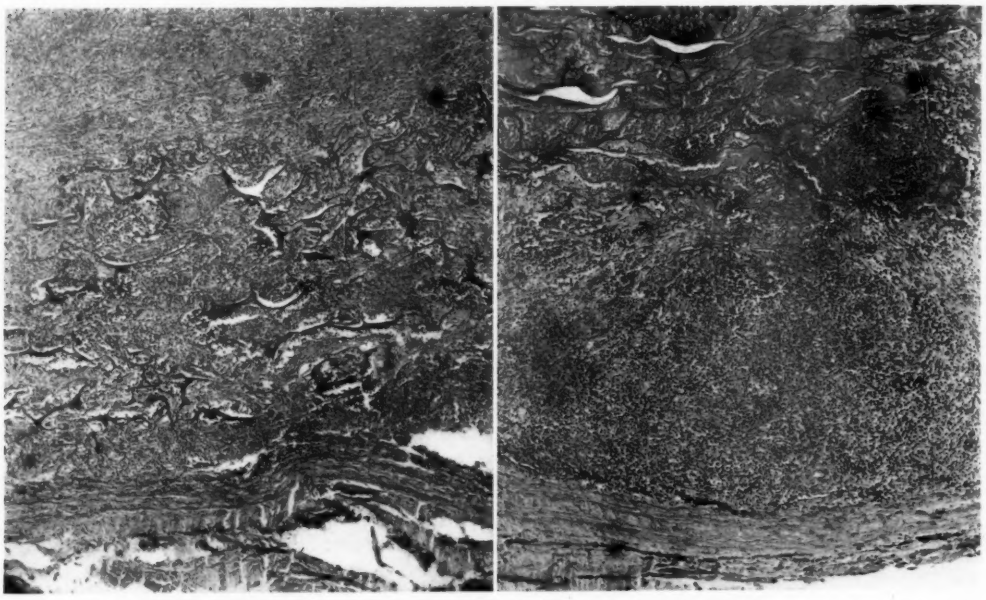

Fig. 2. One week after implantation. a, left, Gelatin sponge; b, right, fibrin foam. Hematoxylin and eosin. ×70.

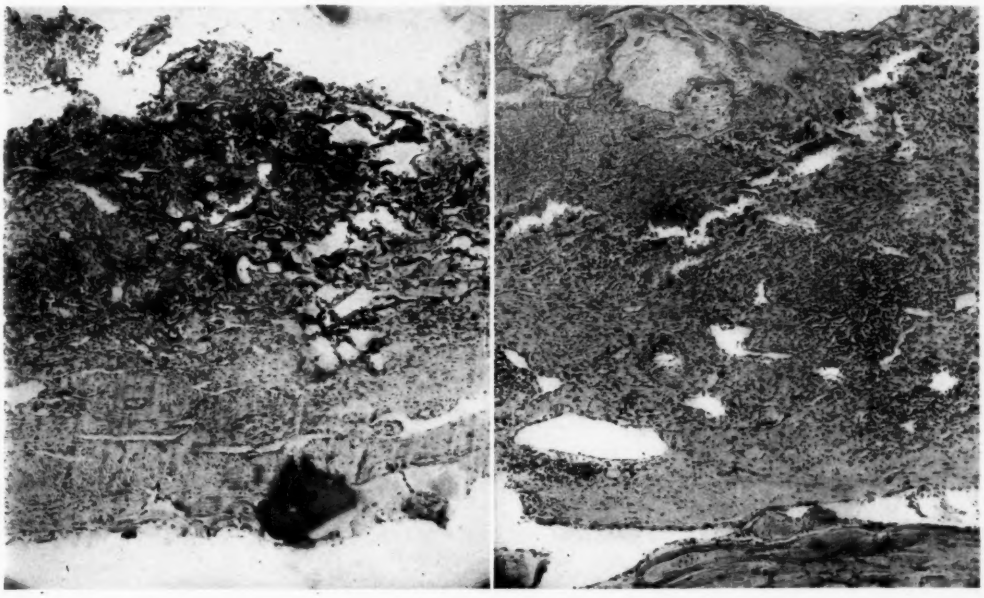

Fig. 3. Two weeks after implantation. a, left, Gelatin sponge; b, right, fibrin foam. Fibroplasia and round cell infiltration. Hematoxylin and eosin. ×70.

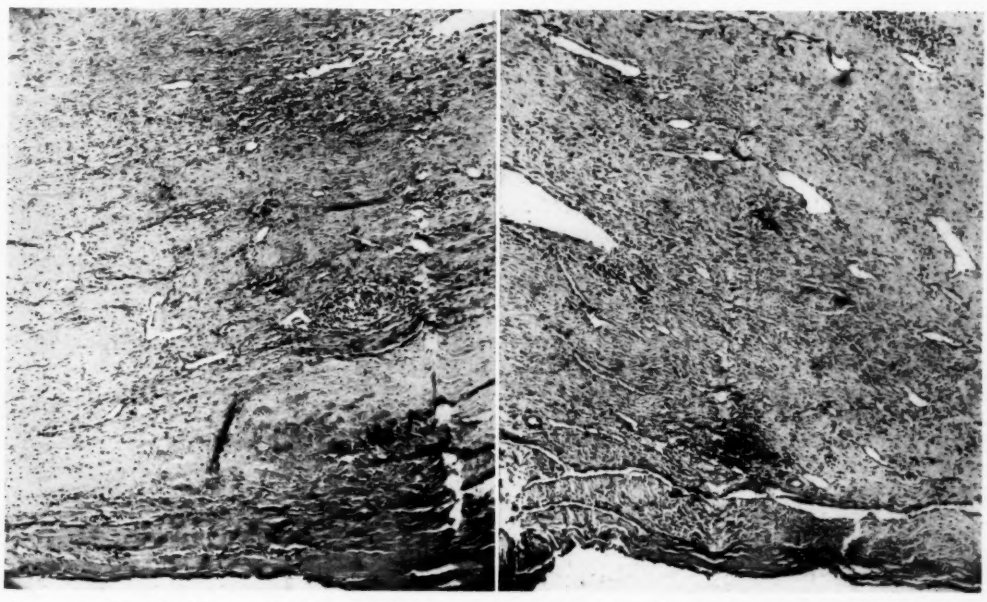

Fig. 4. Four weeks after implantation. a, left, Gelatin sponge; b, right, fibrin foam. Note young blood vessels, denser fibrous tissue and small islands of unabsorbed sponge and foam with surrounding inflammatory reaction. Hematoxylin and eosin. ×70.

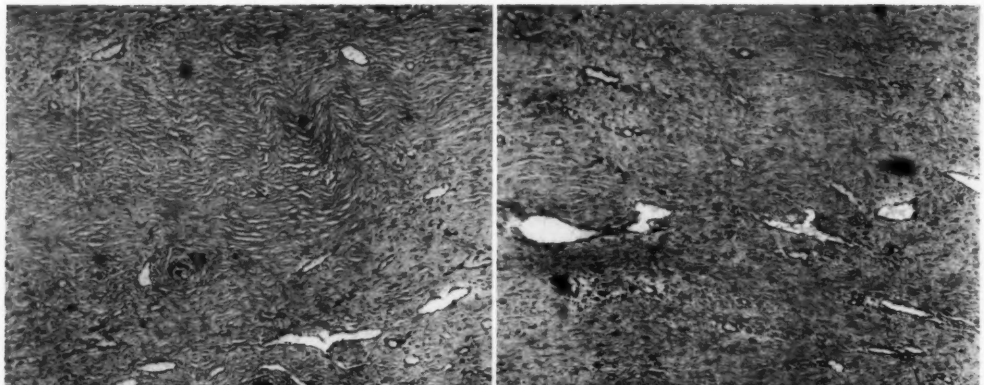

Fig. 5. Six weeks after implantation. a, left, Gelatin sponge; b, right, fibrin foam. Dense elastic tissue is replacing the granulation tissue. Hematoxylin and eosin. ×70.

to the underlying dura. The longitudinal sinus was found to be patent in all animals. The areas of dura upon which the sponge and foam had been placed were removed, fixed in 10 per cent formalin and sectioned for histological study.

Microscopically, the reaction to the two substances and their time of disappearance were quite similar. Comparable sections at the various intervals are shown in the accompanying photomicrographs.

There was an early infiltration of polymorphonuclear leucocytes. The infiltration involved the spaces in the sponge or foam, previously filled with fibrin (Fig. 1). Sometimes there developed a leucocytic mass between dura and foam with less infiltration into the foam itself, as though the latter were relatively impermeable to the cells (Fig. 2, b).

By the end of one week (Fig. 2), infiltration of fibroblasts and round cells was replacing the early inflammatory change and this process was more pronounced at 2 weeks (Fig. 3). At the latter stage considerable absorption of both foam and sponge had taken place and new blood vessels were producing a phase of granulation.

At 4 weeks, both sponge and foam had completely disappeared except for tiny isolated fragments which were surrounded by a mild inflammatory reaction (Fig. 4). Young blood vessels were still present, but the fibrous tissue was growing more dense. At 6 weeks the sites of implantation of foam and sponge were almost completely healed with the formation of plaques of moderately dense elastic tissue (Fig. 5).

In general, the reaction to these materials was little if any more marked than would have been associated with the absorption of a simple hematoma of comparable size. No significant difference between the reactions to the foam and the sponge was detected.

CLINICAL OBSERVATIONS

Reports on the use of gelatin sponge in a total of 272 neurosurgical operations have been received from Dr. Edwin Boldrey, Dr.

THE VALUE OF GELATIN SPONGE AND HUMAN THROMBIN IN NEUROSURGERY

Investigator	Total cases	Results		Comparison with fibrin foam			
		Good	Unsatisfactory	Number of cases	Superior to foam	Inferior to foam	Equal
Coleman	21	20	1	5	5	0	0
Craig	17	16	1	3	3	0	0
Davis	4	4	0	4	3	0	1
Fincher-Swanson	54	53	1	15	4	0	11
Horrax-Poppen	45	45	0	6	6	0	0
Naffziger-Boldrey	39	37	2	19	10	1	8
Penfield-Cone	25	24	1	21	4	0	17
Pilcher	46	46	0	46	33	1	12
Ray	23	23	0	6	5	0	1
Sachs	11	10	1	8	0	1	7
Woodhall-Whitcomb	6	5	1	1	0	0	1
Totals	291	283	8	134	73	3	58

Claude Coleman, Dr. William Cone, Captain William Craig, Dr. Loyal Davis, Dr. Edgar Fincher, Dr. Gilbert Horrax, Dr. Howard Naffziger, Dr. Wilder Penfield, Dr. J. L. Poppen, Dr. Bronson Ray, Dr. Ernest Sachs, Dr. Homer Swanson, Captain B. B. Whitcomb, Lieut. Colonel Barnes Woodhall, and ourselves. In 115 of these procedures, fibrin foam was also employed for comparative purposes. Human thrombin was employed exclusively, since it was desired not to introduce any additional factor which might influence evaluation of the sponge.

The reports have been submitted soon after the operative procedures and have presented the surgeons' impressions of the value of gelatin sponge, saturated with a solution of thrombin, as a hemostatic agent. However, in extensive correspondence, no harmful late effects have been reported, and, in our own 41 cases, none have been observed.

The sponge has proved most useful in the control of epidural venous bleeding, particularly under the bone edges adjacent to an osteoplastic flap, of diffuse oozing in a tumor bed, or epidural bleeding in the spinal canal and in the preparation of a dry bed for a sutured peripheral nerve. Arterial bleeding is seldom controlled unless in such a position that pressure can be maintained.

A summary of the reports received appears in the accompanying table. Every investigator has found the sponge to be satisfactory in the great majority of his cases, and has expressed a highly favorable opinion regarding its usefulness. In 5 of the 8 instances in which it has been reported unsatisfactory, the investigator offered a reason not attributable to the sponge to explain the poor result.

The opinions expressing greater satisfaction with gelatin sponge than with fibrin foam are based entirely, not on the failure of the latter to effect hemostasis, but on the greater ease of handling the sponge. It has no tendency to crumble or fragment, can be cut with a knife or scissors when either wet or dry and retains excellent tensile strength when wet. In only 3 of 115 cases did the surgeon consider the sponge inferior to fibrin foam. It was considered superior in 70 cases but equally satisfactory in 42.

CONCLUSIONS

In view of the observations of Light (5, 6) and of the results reported herein, it seems justifiable to conclude that absorbable gelatin sponge is a safe and efficacious medium for the application of thrombin in the control of venous bleeding in neurosurgical operations. It is usually easier to handle than fibrin foam, and it can be produced in quantity by a simple process from a plentiful and inexpensive substance.

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EXCISION OF THE FRACTURED PATELLA

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BECAUSE of its prominent position at the anterior aspect of the knee, the patella is vulnerable in direct as well as indirect injuries to the knee. In direct injuries, such as a fall on the flexed knee, the patella is particularly prone to fracture. In indirect injuries, such as a sudden violent contraction of the quadriceps, one of four types of defect may occur to cause a disruption of the extensor mechanism of the knee. The patella may fracture; the quadriceps or patellar tendons may rupture; or the tibial tubercle may become avulsed.

Our particular consideration at present is with the fractured patella. Therapy in the other three instances is clear cut. Avulsed tibial tubercles are readily reduced and may be fixed in position by a screw. Ruptures of the quadriceps or patellar tendons require open operation for repair. The end-results in all three of these instances are usually good without disabling sequelae.

THERAPEUTIC PROCEDURES FOR FRACTURED PATELLAE

In the case of the fractured patella, however, therapeutic procedures are not uniform. Many of the following have been used:

1. Rest in bed with adhesive strapping to coapt the patellar fragments.
2. Plaster-of-Paris immobilization.
3. Percutaneous circumferential wiring of the patella with flexible stainless steel wire acting as a pursestring suture.
4. Kirschner wires drilled percutaneously in crucial fashion through the patellar fragments to immobilize them.
5. Open reduction with suture of patellar fragments and quadriceps tendinous expansions. Catgut, silk, linen, fascia lata, kangaroo tendon, and wire have been employed as suture material.
6. Open reduction and fixation of the fragments with nails, screws, or plates.
7. Bone graft in cases of nonunion.
8. Partial excision with suture of the involved quadriceps or patellar tendon to the remaining fragment.
9. Complete excision of the patella.

The mere fact that so many types of treatment have been employed is an indication of the lack of satisfaction with any one of them.

Disadvantages of closed or open reduction. Since the beginning of the 20th century, open reduction has been the method of choice in treating fractures of the patella with wide separation. The incidence of nonunion and fibrous union has been much greater with closed reduction than with the open method. However, even with the latter, bony union is not always obtained. The results did improve after particular care was taken to repair the lacerated quadriceps expansions. But even then nonunion and fibrous union have been too frequent. This fact produces a sense of insecurity in the involved knee, particularly when walking stairs. Some form of external support is often required to control this instability. Frequently in cases with fibrous union and even with bony union refracture occurs, whether treated originally by closed or open reduction. It has been reported that 10 per cent of fractured patellae refracture. This recurrence may take place without actual trauma, but merely following strong sudden contraction of the quadriceps. The majority occur within the first year, but they may occur several years later. A further complication is the malunion of fractured patellae. In many cases the patellar fragments unite with some irregularity of the articular surface. Arthritic changes develop with painful restricted mobility and weak undependable knees. At times it is necessary secondarily to remove the wire suture or even the patella.

Excision of the patella. In view of the complicating sequelae noted which may follow open as well as closed attempts to obtain bony union, excision of the patella has become a popular method of therapy. Partial or com-

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plete excision may be performed depending upon the local findings in each instance. Total patellectomy is particularly indicated in severely comminuted fractures. Compound comminuted fractures due to gunshot wounds may be so badly shattered that nothing but total excision should be considered. Usually the degree of comminution noted at operation is much greater than the roentgenograms indicate. These cases are more commonly seen in the service. In civilian life simple transverse fractures of the patella comprise the large majority of cases. Total patellectomy may even be preferable here originally when one considers the possibility of developing nonunion or fibrous union, union with secondary arthritic changes, union with restricted mobility, and refracture. In some cases the fragments unite with lengthening of the patella which may restrict joint motion. Excision of the patella is being employed in cases of arthritis involving the patella whether there has been a fracture or not.

Advantages of patellectomy. There are many advantages in the treatment of fractured patellae by excision. Patellectomy offers a rapid, progressive, uneventful recovery in practically all instances. This fact holds true even in the compound cases, provided strict adherence to the principles of therapy in such instances is followed. The wounds should be thoroughly débrided and cleansed. Following excision of the patella, the joint capsule should be loosely closed with interrupted sutures. The remaining wound is left open for secondary closure after clinical evidence indicates that there is no infection. With the use of sulfonamides or penicillin locally and parenterally, the incidence of infection can be held to a minimum. This statement is particularly true when the patella has been excised and has thereby been removed as a source of infection. Even in the occasional case of infection complicating compound fractures of the patella, the prognosis for a well functioning mobile knee is better when patellectomy has been performed than when the patella has been permitted to remain.

Postoperative convalescence following patellectomy is much shorter than after open reduction. Patients treated by closed or open reduction require plaster-of-Paris immobilization for approximately 4 to 6 weeks. The period of fixation will vary with the degree of injury, and in open cases, with the suture material used for repair. Following this an indefinite but usually long period of physical therapy and reconditioning is required to obtain free motion of the knee and strong quadriceps power. It may be 4 to 6 months before these patients return to strenuous activity. Even then the knee may be symptomatic and refracture may occur. Conversely, in the healing of repaired fractures, excessive regenerative changes may take place. Calcium is laid down giving the appearance of an abnormally large patella. In either case there is usually some loss of joint motion. Generally the patella is considered to have little osteogenetic property.

Following patellectomy, however, the patient may be walking without dressings or support at the end of 2 to 3 weeks. Motion and quadriceps exercises can be instituted shortly after operation and a normally mobile and stable knee with complete function can be obtained within 6 to 8 weeks. Rehabilitation is progressive and rapid. In 2 of the cases to be reported in which the patella was fractured by gunshot wound, the missile also damaged the articular surface of one of the femoral condyles. Yet there was no restriction of motion and no disability. One of these patients, a paratrooper, returned to jump duty. Patellectomy does not adversely affect motion, strength, or stability of the knee. In soldiers with unilateral patellar fractures and complicated femoral or tibial fractures of the opposite extremity, excision of the patella permits them early ambulation with weight bearing on the patellectomized extremity.

Partial excision of the patella may be indicated in cases of comminution at either pole of the bone. The small fragments are removed and the patellar or quadriceps tendon is sutured to and through the remaining large fragment. Normally it is the lower pole of the patella that is comminuted and excised. This circumstance leaves a large portion of the patella proximally to protect the femoral condyles when kneeling. In these cases union of the tendinous structures alone is involved and

the required time of immobilization is again shorter than when reduction is attempted. Approximately 3 to 4 weeks is adequate.

Disadvantages of patellectomy; regeneration of the patella. Resection of the patella is said to have several disadvantages. One is that it removes the normal protection for the femoral condyles. Dobbie and Ryerson, however, quote R. Brooke of England as stating that the patella is merely a morphological remnant phylogenically inherited and that it is tending to undergo reduction in size and to disappear. Brooke claims that it plays no functional part and that in its absence the efficiency of the knee joint is increased both in rapidity of movement and power. Nevertheless, following patellectomy the articular cartilage over the femoral condyles and intercondylar space anteriorly is left exposed to direct trauma. Occasionally there may be pain when kneeling. Regeneration of a new patella in kind, however, generally affords adequate protection.

Dobbie and Ryerson quote Carey, Zeit, and McGrath in their published findings relating to the regeneration of the patella in dogs. Regeneration is said to occur under adequate mechanical conditions. The requisites are a normally mobile joint following patellectomy and adequate repair of the soft parts. Evidence of regeneration experimentally in dogs is said to appear roentgenographically in from 17 to 60 days. When adequate conditions do not prevail and the knee is not mobile due to joint fixation, regeneration fails to take place. In other words, the actual existence of a patella is based upon the functional need of a sesamoid bone at the site of pressure and tension where the quadriceps tendon glides over the femoral condyles in a freely movable joint. This observation appears to be substantiated by the cartilaginous and bone atrophy of the patella in cases in which the mobility of the knee is lost either by fusion or arthrodesis. There is no record, however, of total and complete regeneration of a new patella. In many cases, actually, there is no roentgenographic evidence of even partial regeneration of a new patella. Yet clinically one can palpate a firm round or oval movable body within the quadriceps tendon at the site of the old patella. This body may consist of cartilage or fibrocartilage and therefore remain radiolucent. However, it appears to function as well as a normal patella and affords adequate protection to the femoral condylar cartilage.

A second objection to the patellectomy is said to be the cosmetic change in the knee. It is true that the prominence of the normal patella is lost and even in case of patellar regeneration there is failure completely to recover the normal topography of the knee. However, this objection is insignificant compared with the benefits derived from excision of the bone in properly selected cases.

A third objection to patellectomy is said to be the diminution of pulley action which the patella normally produces during active extension of the knee. The patella does carry the quadriceps tendon away from the femoral condyles and theoretically should increase the efficiency of the muscle by its leverage action. However, one cannot disregard the excellently functioning powerful knees that are seen clinically following excision of the patella. The uniformly good results following patellectomy fully justify the theoretically mathematical diminution of leverage action of the quadriceps. This statement is especially true when one considers the possible untoward sequelae that may result in attempting to obtain bony union of the patella. Besides, regeneration of the patella tends to minimize and restore the theoretical loss of the leverage action.

Anatomy. In order fully to appreciate the operative technique, consideration of the local anatomy may be in order. The quadriceps femoris, the great extensor of the leg, is subdivided into four portions: the rectus femoris, the vastus lateralis, the vastus medialis, and the vastus intermedius. All subdivisions converge at the distal end of the thigh anteriorly to form the quadriceps tendon which passes over the anterior surface of the patella and continues as the patellar tendon. The quadriceps tendon attaches to the base, anterior surface, and lateral borders of the patella. The patellar tendon inserts into the tibial tuberosity. In addition, the quadriceps tendon gives off an expansion on either side of the patella to form the medial and lateral patellar

retinacula. These blend with the articular capsule and insert into the proximal end of the tibia on either side of the tuberosity. In fractures of the patella these expansions may be widely lacerated, and it is important that they be thoroughly repaired. Thus it is seen that the patella may be regarded as a sesamoid bone, developed within the tendon of the quadriceps.

Optimum time of operation. The interval between injury and operation varies with the general condition of the patient. In compound fractures, thorough débridement and patellectomy should be performed as soon as it is safely possible. The earlier the wound is cleansed the less tendency is there for it to become infected. In simple fractures also there appears to be no advantage in operative delay. If there is no significant contraindication to immediate operation, it should be performed directly after admission to the hospital. Hemorrhage can thereby be controlled thus avoiding unnecessary edema and infiltration of the soft tissues. Some surgeons feel however, that when the soft tissues are moderately traumatized, immediate operation will further damage them and jeopardize primary healing. They, therefore, prefer to wait about a week before operating. The decision primarily is a personal one, but generally speaking operative delay offers no advantage.

TECHNIQUE OF OPERATION

In *compound gunshot wound fractures*, whether penetrating or perforating, the wounds should be adequately exposed in order to permit thorough débridement. The author has had occasion to treat perforating gunshot wounds with compound fractures when the roentgenograms were negative for foreign bodies. The wounds of entrance and exit were small, yet exposure of them revealed chocolate discoloration of muscle indicative of necrosis. In such cases it is imperative that this discolored necrotic tissue be excised, since it may act as an excellent medium for the growth of anaerobic organisms. Following débridement and patellectomy, the joint capsule should be loosely closed with interrupted sutures and the wound lightly packed with vaseline gauze. Secondary closure can be performed in approximately 1 week provided there is no evidence of infection.

Fig. 1. Case 1. Left, comminuted fracture left patella following glider crash, October 19, 1943. Right, following excision of distal comminuted fragments.

In *simple fractures* either a vertical or transverse incision is employed centered over the patella. The former requires wide dissection laterally of skinfascial flaps in order to expose the quadriceps expansions. The latter approach permits an easier exposure of the patellar retinacula. It is also preferable since it can be made within the skin crease and therefore, will heal with less tendency to thick scarring which may prevent free flexion of the knee. Blood clot is removed and the patellar fragments excised, care being taken to retain intact the quadriceps tendon anterior to the patellar fragments. The frayed edges of the extensor tendon and its expansions are then débrided and repaired. Interrupted sutures are employed beginning at both ends of the rent in the expansions and working centrally to tendon. This procedure makes closure much easier; remaining wound is closed in layers.

Postoperative care. It is preferable to immobilize the knee with a posterior splint for 7 to 10 days. However, a firm flannel or stockinette bandage may also be employed. The important factor is that acute flexion of the knee be avoided until the repaired tendon is well healed. This healing requires approximately 3 weeks. Postoperative immobilization is not objectionable in cases of patellectomy. One

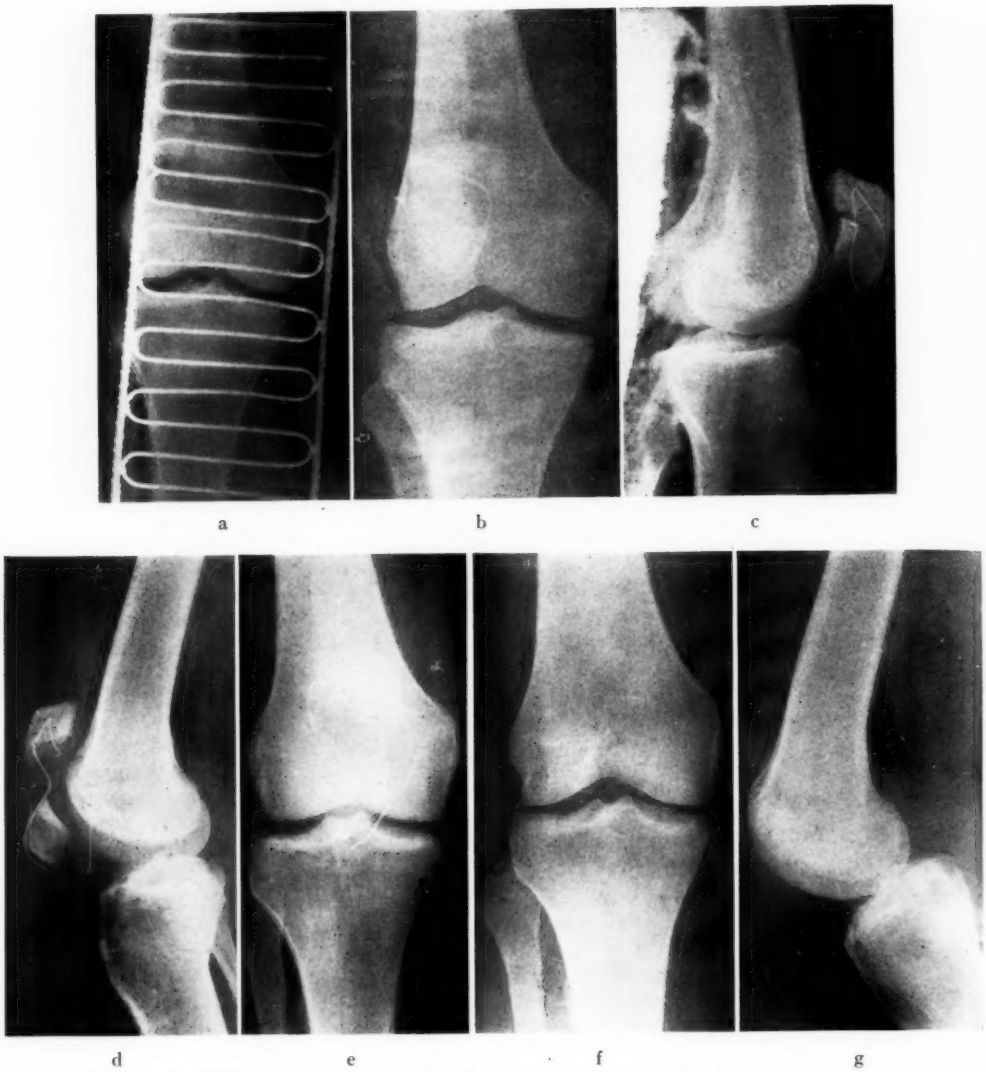


Fig. 2. Case 3. a, Compound comminuted fracture right patella, November 30, 1943, following "peep" accident. b and c, Following immediate débridement and wiring. d and e, Wide separation of patellar fragments on February 24, 1944, almost 3 months later, induced by partial weight bearing on crutches. f and g, Appearance of knee on September 22, 1944, almost 7 months after patellectomy. Function of knee is normal.

of our patients remained in a plaster-of-Paris cast for 7 weeks during his evacuation to the zone of interior. Yet he has a strong, well functioning knee with a full range of motion. When the splint is removed at the end of the first week, the patient may be encouraged to begin flexing the knee gently. After the third week complete flexion should be strived for. Quadriceps setting exercises are also instituted upon removal of the splint.

Weight bearing with the aid of a cane and posterior knee splint may be permitted at the

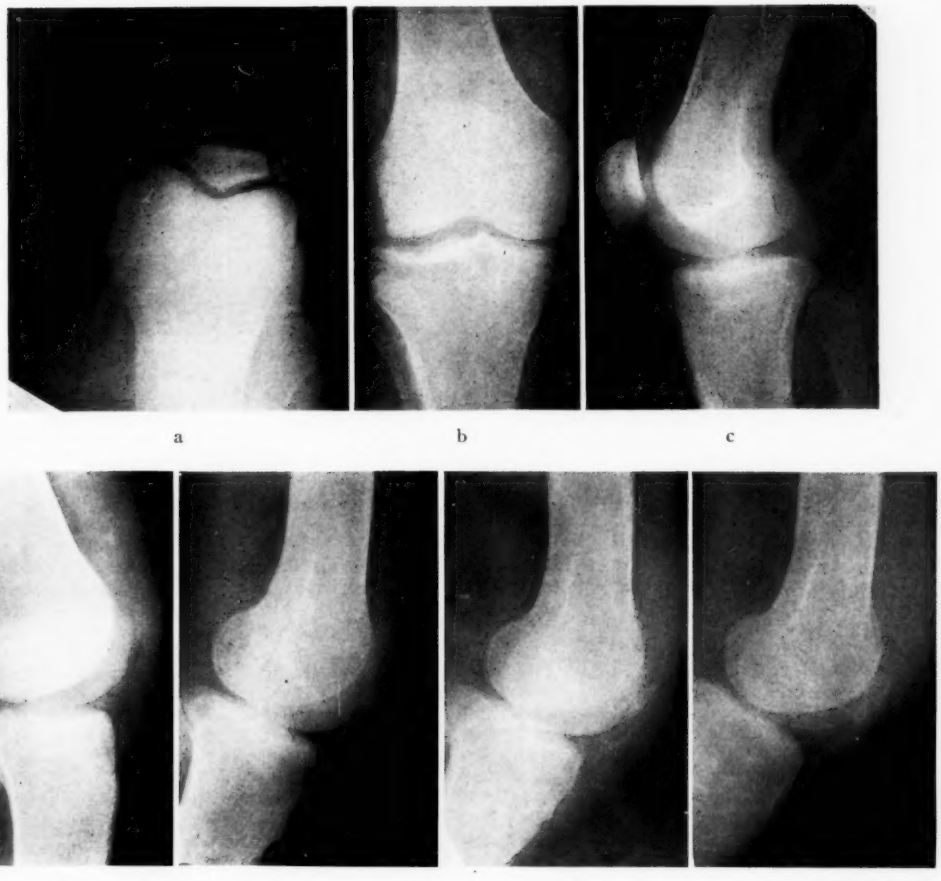
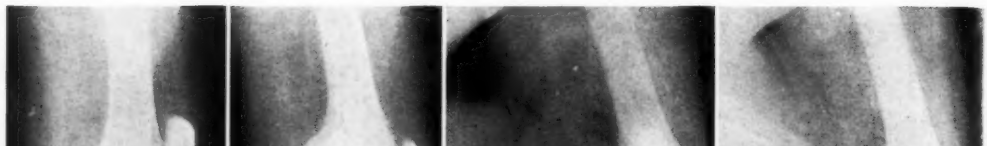


Fig 3. Case 6. a, b, c, Longitudinal fracture of the right patella, December 15, 1943, following fall from a horse. d, e, f, g, The progressive regeneration of the patella as noted in the lateral views which were taken on May 19, 1944, July 15, 1944, August 14, 1944, and September 30, 1944.

end of 1 week. However, full weight bearing without support should be delayed until the third week. By the end of 6 to 8 weeks the patient should be able to walk normally for a full day, on level ground as well as up and down stairs. One of our patients returned to parachute jump status at the end of 3 months. Complete rehabilitation is generally obtained at the end of 10 to 12 weeks.

END-RESULTS

In cases of total excision of the patella the end-results are generally excellent. The patients obtain a normally functioning knee with complete range of motion, normal stability, and powerful extension. They are able to walk long distances and can manage stairs without difficulty. They are able to squat fully on both legs and arise with ease. They can even squat partially on the involved extremity alone and arise to the erect position without undue effort. One patient could squat completely and arise on the involved extremity alone. Kneeling may cause discomfort temporarily, but usually this subsides in time. One of the cases to be reported developed an



a b c d

Fig. 4. Roentgenograms of a normal knee at 180, 135, 90, and 45 degrees, indicating progressive motion of the patella for the protection of the femoral condyles during flexion of the knee.

infection of the knee joint postoperatively, yet he obtained a well functioning and almost completely movable knee. Had the patella remained, I doubt whether such a good result would have been obtained. In the presence of infection the patella usually becomes fixed to the femur either partially or completely and thereby restricts mobility of the joint.

CASE REPORTS

CASE 1. Patient was admitted to Station Hospital, Camp Mackall, North Carolina, on October 19, 1943, following a glider crash. He sustained a fracture dislocation of the right ankle, a comminuted fracture of the left patella, a fracture of the posterior border of the left lateral tibial condyle, and a laceration just distal to the left knee anteriorly. Marked swelling and ecchymosis of the right ankle and left knee were present. In view of the general as well as local condition of the patient, reduction of both sites was necessarily postponed. The right ankle was subsequently reduced by the closed method. Open operation was performed on the left knee and the distal comminuted fragments of the patella excised. The patellar tendon was sutured to the fractured surface of the patella with fascia lata carried through two drill holes in the bone. They began on the anterior aspect of the patella and emerged on the raw fractured surface, care being taken not to injure the cartilaginous surface. A rent was found in the medial quadriceps expansion and it was repaired. Plaster-of Paris immobilization was employed for 15 days. Within 1 month thereafter he had almost complete range of motion in the knee and he could walk somewhat without support. He was then transferred to a reconditioning center preparatory to return to duty. Partial resection of the patella is indicated in cases such as this in which the greater portion of the patella remains intact.

CASE 2. A middle aged woman was treated during civilian practice at Sydenham Hospital, New York, in 1937. Patient presented a transverse fracture of the patella with proximal and distal fragments about equal in size. An open reduction was performed. The patellar fragments were sutured with kangaroo tendon and the quadriceps expansions with chromic catgut. Plaster-of-Paris immobilization was employed for about 6 weeks. With physical therapy and reconditioning, the patient gradually returned to her normal activities. Clinically and roentgenologically the patella appeared to be well united. Yet about 5 months later she refractured the same patella while stepping off a curbstone. There was no injury this time except for possible sudden strong quadriceps contraction. This time the patella was totally excised and the patient made an uneventful recovery. Knee function was normal and strong and mobility was complete.

CASE 3. Soldier was injured on November 30, 1943, when the "peep" he was driving collided with a "caterpillar" in Alaska. He sustained a compound comminuted fracture of the left femur and a compound comminuted fracture of the right patella. Palpation revealed two distinct and widely separated fragments in the right knee. Immediate débridement was performed of both wounds. The right patella was reduced and maintained with stainless steel wire. A posterior plaster-of-Paris splint was applied for immobilization. Skeletal traction was employed for the left femoral fracture.

Plaster immobilization was removed from the right knee after 24 days and the patient permitted to exercise the knee in bed. Skeletal traction was removed from the left femur on February 4, 1944, and the patient allowed up on crutches for short intervals on February 20. On February 24 while standing at his bedside supported by his crutches, he felt a sudden snap and pain in the right knee which gave way beneath him. X-ray films revealed the fact that the stainless steel wire had loosened and the patellar frag-

ments again became widely separated. This separation occurred 3 months after the original injury. The following day the patellar fragments were completely excised and the tendons approximated and sutured. There was no evidence of callus at operation.

At present the patient has a strong, well functioning right knee. He is able to balance and squat partially on the right lower extremity alone and then resume the erect position. He is able to squat completely on both lower extremities without difficulty. Motion of the knee is complete and stability is normal. He is able to hop on the right foot without buckling of the knee. Kneeling on a hard surface causes mild discomfort.

CASE 4. Soldier was injured by shrapnel on May 16, 1944, at Anzio, Italy, sustaining a compound comminuted fracture of the left patella. At operation on May 17, the patella was found to be comminuted more than the roentgenograms had indicated. It was therefore excised. A large piece of shrapnel was found in the infrapatella fat pad in the anterior compartment of the knee joint. It had gouged out an area 1.5 centimeters in diameter from the lateral femoral condyle. The foreign body was removed and the edges of the articular defect smoothed. The joint was irrigated and 10,000 units of penicillin instilled within it. The synovia was closed with interrupted sutures and the remainder of the wound gently packed with vaseline gauze. The leg was immobilized in plaster. The patient was given 25,000 units of penicillin intramuscularly every 3 hours for a total of 825,000 units in 100 hours.

On May 27 a secondary closure of the wound was performed. The quadriceps and patellar tendons were coapted and sutured and the joint capsule closed. The remainder of the wound was closed in layers. Plaster-of-Paris immobilization was employed. This plaster remained on throughout the patient's evacuation to the zone of interior. It was removed on July 14, 7 weeks after application. At that time knee motion was possible only from 180 to 160 degrees. At present his range of motion is from 180 to 40 degrees with quadriceps power of 4 plus. Stability of the knee is good and patient is able to walk quite well. On palpation one gains the impression that there is regeneration of a small patella. However, this regeneration is not visible in the x-ray films. Patient can balance himself well on the involved leg, squat partially and resume the erect position without difficulty. With weight distributed on both feet he can squat almost completely. He is being reconditioned for return to duty.

CASE 5. Paratrooper was admitted to Station Hospital, Camp Mackall, North Carolina, on December 1, 1943, with a perforating .45 caliber bullet wound through the right knee. He sustained a comminuted fracture of the proximal third of the patella. Roentgenograms of the knee also revealed a defect in the articular surface of the lateral femoral condyle.

The entrance and exit wounds were enlarged and débrided. In addition to the comminution of the patella noted in the roentgenograms, there was also noted at operation a complete longitudinal fracture. The patella was excised *in toto* and the defect in the femoral condyle smoothed. The joint was flushed with sodium sulfathiazole solution. Plaster-of-Paris immobilization was employed for 1 week. About 3 weeks later the patient began to walk. He was last seen by me on February 29, 1944, at which time he was back on full jump status. He had a complete range of painless motion in the knee and his quadriceps power was excellent. Stability of the knee was normal. Patient was able to balance and squat completely on the involved leg alone and return to the erect position without difficulty. He was able to walk stairs with ease. His knee was functionally as normal as before his injury.

CASE 6. Soldier fell off a horse on December 15, 1943, while in New Zealand and sustained a longitudinal fracture of the lateral portion of the right patella. He was treated with bed rest and plaster-of-Paris immobilization for 2 weeks. He was then permitted up with crutches and gradually walked without support. He returned to duty but the pain in the knee increased. Check-up roentgenograms taken on April 15, 1944, revealed nonunion of the fracture. Accordingly, on April 25 patellectomy was performed. On May 4, 1944, he began to run an elevated temperature and on May 23 the knee was incised and seropurulent material obtained. On July 19 the knee was manipulated. When examined by me on September 26, he presented a fairly good knee. He walked without a limp and stability of the knee was normal. He could balance and squat partially on the involved leg alone, returning to the erect position. There was some restriction of motion which was possible from 180 to 115 degrees. Quadriceps power rated a 4 plus. On palpation one gained the impression that an indefinitely outlined regenerated patella was present. Roentgenograms substantiated the progressive deposition of calcium within the quadriceps and patellar tendons.

Knee joint infections without patellectomy usually result in a much more disabling and stiffer joint than this patient has. The patella usually becomes fixed to the femur and causes marked restriction of motion. Excision of the patella in this case has permitted a more freely movable and useful joint despite the complicating infection.

CONCLUSIONS

1. The treatment of fractured patellae in the past by so many methods is indicative of dissatisfaction with all of them.

2. When one considers the possibility of fibrous union or nonunion, union with restricted

mobility and instability, and union with secondary arthritic changes, one notes the shortcomings of open as well as closed reduction of the patella.

3. The high incidence of refracture of the patella, even following open reduction, reveals the need for a more effective method of treatment.

4. Excision of the patella, either partial or complete, is the method of choice in fractures.

5. Partial excision with removal of the small comminuted fragments alone is indicated only when a large uninvolved portion of the patella can be left *in situ*.

6. In all other instances of fracture total excision is preferable for the following reasons: (a) Rapid progressive uneventful recovery usually ensues; (b) postoperative immobilization and convalescence are shortened; (c) strong, stable, and freely movable knee joints are generally obtained; (d) even when complicating infections occur, the prognosis is better when patellectomy has been performed; (e) excision of the patella does not impair the efficiency of the knee.

7. Regeneration in kind may occur following excision of the patella to protect the exposed femoral condyles.

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INACTIVATION OF PENICILLIN BY VARIOUS GRAM NEGATIVE BACTERIA

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ALTHOUGH the majority of infections seen by the surgeon are caused by the staphylococcus and the streptococcus, many are mixed infections produced by these and various other bacteria, particularly the gram negative bacilli. In the treatment of established infections of surface wounds and abscesses, pure staphylococcal or streptococcal infections have responded much more rapidly and completely to general or topical penicillin therapy than did mixed infections. The course of many of the mixed infections seemed to be completely unaffected by penicillin, and even the staphylococci and streptococci remained present in large numbers in the exudates. This fact suggested that the penicillin was being inactivated or destroyed in the infected area probably by the action of the various gram negative bacteria. To explain these differences of response to penicillin therapy a study was undertaken to measure (1) the effect of penicillin on the growth of the gram negative bacilli frequently found in infected wounds, and (2) the effect of various gram negative bacilli on the activity of penicillin.

It is well known that penicillin is a labile substance which is destroyed by heat, prolonged exposure to the air, and oxidizing or reducing agents. In addition, Abraham and Chain have found that extracts of Escherichia coli prepared by crushing a suspension of the organisms in a bacterial crushing mill destroyed the bacteriostatic property of penicillin. They believed the active substance in these extracts to be an enzyme because it was not dialyzable through a cellophane membrane and because it was inactivated by heating at 90 degrees C. for 5 minutes or incubation with papain.

From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital. The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Cincinnati.

METHODS

The gram negative bacteria commonly found in infected wounds, burns, or deeper abscesses are Escherichia coli, Bacillus pyocyaneus, Aerobacter aerogenes, Bacillus proteus, and Bacillus alkaligenes fecalis. Representative strains of each of these bacteria were obtained from infected wounds, and cultures of each in broth were used throughout the experiments.

In the first group of experiments six series of culture tubes of broth media containing various concentrations of sodium penicillin from 0.005 to 5000 units per cubic centimeter were prepared. Five of the series were then inoculated with 0.1 cubic centimeter of an 18 hour culture of one of the various gram negative bacteria, and the sixth with 0.1 cubic centimeter of an 18 hour culture of a susceptible strain of hemolytic Staphylococcus aureus which was used as a control. After 4, 8, 12, 16, and 20 hour periods of incubation, the effect of penicillin on the rate and amount of growth was determined with the aid of a turbidimeter.

In the second group of experiments the effect of the various gram negative bacilli on penicillin was studied *in vitro*. Tubes of broth media containing 20 units of penicillin per cubic centimeter where inoculated with 0.1 cubic centimeter of an 18 hour culture of one of the gram negative bacilli and incubated at 4, 8, 12, 16, and 20 hours, respectively. Another tube containing an equal number of units of penicillin per cubic centimeter was used as a control and incubated for 20 hours without bacterial inoculation. After the various periods of incubation, the cultures were passed through a Berkefeld filter to remove the bacilli. The antibacterial activity of the bacterial free filtrates was then measured for the hemolytic Staphylococcus aureus by determining the greatest dilution at which growth was inhibited.

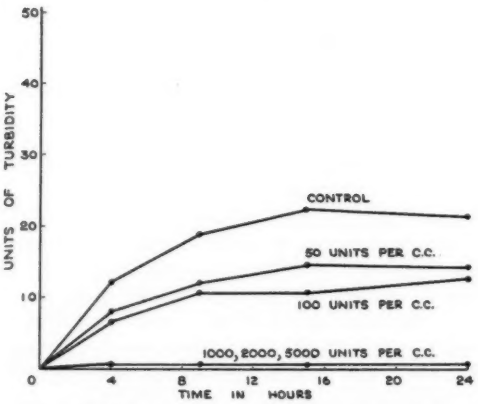

Fig. 1. Inhibitory effect of higher concentrations of penicillin on one strain of Escherichia coli.

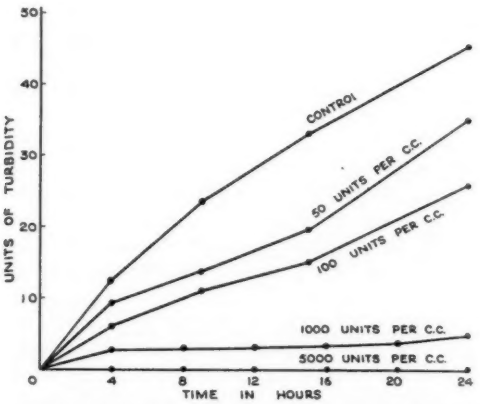

Fig. 2. Inhibitory effect of higher concentrations of penicillin on another strain of Escherichia coli.

RESULTS

Effect of penicillin on the rate and amount of growth of gram negative bacilli. When inoculations of Escherichia coli, Bacillus pyocyaneus, Aerobacter aerogenes, Bacillus proteus, and Bacillus alkaligenes fecalis were made into five series of culture tubes containing concentrations of penicillin from 0.009 to 20.0 units per cubic centimeter of beef infusion broth, the effect of penicillin after incubation for 18 hours is shown in Table I. Little or no inhibitory action on the growth of Escherichia coli, Bacillus pyocyaneus, Aerobacter aerogenes, and Bacillus proteus occurred. On the other hand Bacillus alkaligenes fecalis was almost completely inhibited by 0.039 units of penicillin per cubic centimeter. Further studies on four other strains of Bacillus alkaligenes fecalis have shown all to be sensitive to the action of penicillin. The sensitivity of the hemolytic Staphylococcus aureus was used as a control for the purpose of testing the activity of penicillin.

TABLE I.—EFFECT OF PENICILLIN AFTER INCUBATION FOR 18 HOURS

Concentration	E. Coli	B. Pyocyaneus	A. Aerogenes	B. Proteus	B. Alkaligenes fecalis	Staph. aureus (Control)
20.000	++++	++++	++++	++++	–	–
10.000	++++	++++	++++	++++	–	–
5.000	++++	++++	++++	++++	–	–
2.500	++++	++++	++++	++++	–	–
1.250	++++	++++	++++	++++	–	–
0.625	++++	++++	++++	++++	–	–
0.312	++++	++++	++++	++++	–	–
0.156	++++	++++	++++	++++	–	–
0.078	++++	++++	++++	++++	–	–
0.039	++++	++++	++++	++++	+	++
0.019	++++	++++	++++	++++	+++	++++
0.009	++++	++++	++++	++++	++++	++++

Showing lack of inhibitory action of lower concentrations of penicillin on the growth of various gram negative bacilli using hemolytic Staphylococcus aureus as a control.

If higher concentrations of penicillin were used such as 50, 100, 250, 500, 1000, 2000, and 5000 units per cubic centimeter of media a definite inhibitory effect on the rate and amount of growth of Escherichia coli was apparent. If the amount of growth was measured in units of turbidity on the turbidimeter at intervals of 4 hours, it was found that the inhibitory action increased with the concentrations of penicillin. This fact is shown graphically in Figures 1 and 2. The degree of inhibition varied with the strain of Escherichia coli; in Figure 1 it will be noted that growth was completely inhibited by 1000 units per cubic centimeter and in Figure 2 by 5000 units per cubic centimeter.

The inhibitory effect was of a bacteriostatic nature, since subcultures were always positive.

A similar but less marked inhibition was caused by higher concentrations of penicillin on the growth of Aerobacter aerogenes (Fig. 3).

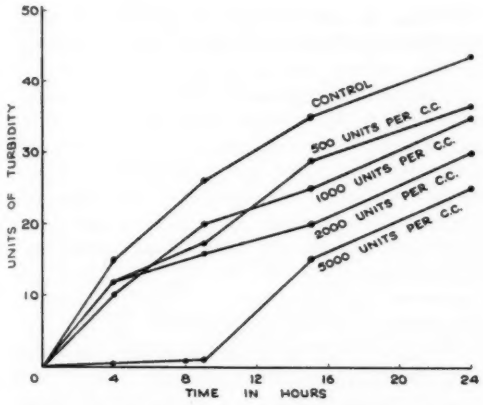

Fig. 3. Inhibitory effect of higher concentrations of penicillin on one strain of Aerobacter aerogenes.

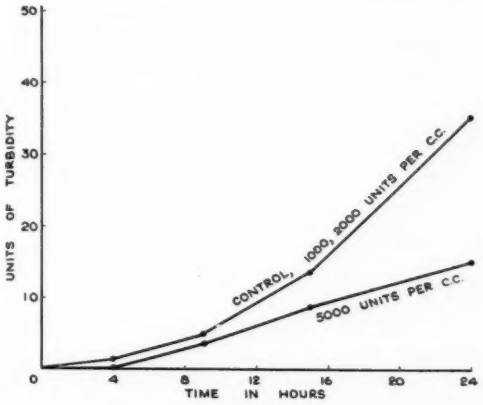

Fig. 4. Marked resistance of Bacillus pyocyaneus to higher concentrations of penicillin.

On the other hand, many of the strains of Bacillus pyocyaneus tested showed marked resistance to concentrations of penicillin as high as 5000 units per cubic centimeter (Fig. 4).

The effect of gram negative bacilli on penicillin. After tubes of broth media containing 20 units of penicillin per cubic centimeter were inoculated with Escherichia coli, incubated for 4, 8, 12, 16, and 20 hours and then passed through a Berkefeld filter to remove the bacilli, the antibacterial activity of the filtrate for the hemolytic Staphylococcus aureus was measured by determining the greatest dilution at which bacterial growth was inhibited. It was found that the penicillin activity had been progressively destroyed after 4, 8, and 12 hours' growth of the colon bacilli. The destruction was practically complete at 12 hours. The control retained its marked antibacterial action for the hemolytic Staphylococcus aureus after 20 hours' incubation and filtration.

The same experiment was repeated with Bacillus pyocyaneus and a similar progressive

TABLE II.—SHOWING THE DESTRUCTIVE ACTION OF CULTURES OF ESCHERICHIA COLI ON PENICILLIN

Duration of incubation with Bacillus coli in hours

Dilutions* Amount	4	8	12	16	20	Control
1:1	−	−	+	++++	++++	−
1:2	−	−	+	++++	++++	−
1:4	−	−	++	++++	++++	−
1:8	−	−	++	++++	++++	−
1:16	−	+	+++	++++	++++	−
1:32	−	++	++++	++++	++++	−
1:64	+	+++	++++	++++	++++	−
1:128	+++	++++	++++	++++	++++	−
1:256	++++	++++	++++	++++	++++	−
1:512	++++	++++	++++	++++	++++	++
1:1024	++++	++++	++++	++++	++++	++++

*Bacterial free filtrates containing penicillin after incubation with Escherichia coli.

TABLE III.—SHOWING DESTRUCTIVE ACTION OF CULTURES OF BACILLUS PYOCYANEUS ON PENICILLIN

Duration of incubation with Bacillus pyocyaneus in hours

Dilutions* Amount	4	8	12	16	Control
1:1	−	−	−	++	−
1:2	−	−	+	++	−
1:4	−	−	++	+++	−
1:8	−	+	+++	+++	−
1:16	+	++	+++	+++	−
1:32	++	+++	++++	++++	−
1:64	++	+++	++++	++++	−
1:128	+++	+++	++++	++++	−
1:256	++++	++++	++++	++++	−
1:512	++++	++++	++++	++++	+++
1:1024	++++	++++	++++	++++	++++

*Bacterial free filtrates containing penicillin after incubation with Bacillus pyocyaneus.

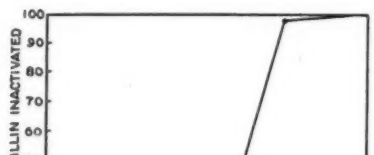

Fig. 5. Percentage and rate of penicillin inactivation by actively growing cultures of Bacillus pyocyaneus.

destruction of penicillin was noted (Table III).

When the percentage and rate of penicillin inactivation were charted, it was noted that approximately 98 per cent of the penicillin was destroyed within 12 hours and almost all of this during the 8 to 12 hour period by Escherichia coli and Bacillus pyocyaneus (Fig. 5).

Aerobacter aerogenes produced a similar but lesser degree of penicillin inhibition (Table IV).

On the other hand Bacillus proteus had but little destructive effect on the activity of penicillin (Table V).

When a 24 hour culture of Escherichia coli, grown in the absence of penicillin, was passed through a filter, the bacterial free filtrate did not contain a substance which inactivated penicillin. At the end of 4 and 16 hours' incubation with penicillin, no significant loss of antibacterial activity for the hemolytic Staphylococcus aureus was noted. Likewise no significant destruction of penicillin was produced by the action of heat killed cultures of Escherichia coli.

ANALYSIS OF STUDY

Escherichia coli, Bacillus pyocyaneus, Aerobacter aerogenes, and Bacillus proteus are frequently found in infected wounds and burns in association with staphylococci and other bacteria. They are completely resistant to the action of 20 units of penicillin per cubic centimeter, a concentration greater than any produced in the blood and tissues by parenteral administration. High concentrations of 50, 100, 250, 500, 1000, 2000, and 5000 units have a definite but incomplete inhibitory effect on the rate and amount of growth of many of these bacteria, although this effect varies in degree with different strains of the same organism. The action is bacteriostatic since the inhibited bacilli grow profusely on subcultivation in penicillin free media. Five strains of Bacillus alkaligenes fecalis, on the other hand, were very sensitive to the action of penicillin.

TABLE IV.—SHOWING EFFECT OF CULTURES OF AEROBACTER AEROGENES ON PENICILLIN

	Duration of incubation with Aerobacter aerogenes in hours				
Dilutions* Amount	4	8	12	16	Control
1:1	−	−	−	−	−
1:2	−	−	−	−	−
1:4	−	−	−	+	−
1:8	−	−	+	++	−
1:16	−	+	++	++	−
1:32	++	++	++	++++	−
1:64	++	+++	++++	++++	−
1:128	+++	++++	++++	++++	−
1:256	++++	++++	++++	++++	−
1:512	++++	++++	++++	++++	+++
1:1024	++++	++++	++++	++++	++++

*Bacterial free filtrates containing penicillin after incubation with Aerobacter aerogenes.

TABLE V.—SHOWING EFFECT OF CULTURES OF BACILLUS PROTEUS ON PENICILLIN

	Duration of incubation with Bacillus proteus in hours				
Dilutions* Amount	4	8	12	16	Control
1:1	−	−	−	−	−
1:2	−	−	−	−	−
1:4	−	−	−	−	−
1:8	−	−	−	−	−
1:16	−	−	−	−	−
1:32	−	−	−	−	−
1:64	−	−	−	−	−
1:128	+	++	++	++	−
1:256	+	++++	++++	+++	−−
1:512	+++	++++	++++	++++	+++
1:1024	++++	++++	++++	++++	++++

*Bacterial free filtrates containing penicillin after incubation with Bacillus proteus.

These studies explain at least in part the frequent failure of penicillin therapy in mixed infections of wounds.

To overcome the destructive effect on penicillin produced by the gram negative bacteria, these experiments suggest several principles in the local therapy of infected wounds:

1. The removal of as many bacteria from the wounds as possible immediately preceding the topical application of penicillin. The mechanical removal of devitalized tissue and purulent exudate by incision and drainage, aspirations, or irrigation greatly reduces the number of gram negative bacteria at the time of the topical application of penicillin. Devitalized tissue invites and harbors gram negative bacillary infection and its removal by mechanical or chemical means would seem to be particularly important.

2. The local application of higher concentrations of penicillin up to 1000 or 2000 units per cubic centimeter to inhibit as much as possible the growth of the gram negative bacilli and their destructive action.

3. Application of penicillin at frequent intervals of 8 hours or less to compensate for the amount destroyed by the gram negative bacilli and to insure a level therapeutically effective for the penicillin sensitive bacteria also infecting the wound.

CONCLUSIONS

1. Various gram negative bacilli commonly found in infected wounds were very resistant to the action of penicillin in concentrations up to 20 units per cubic centimeter. Higher concentrations up to 2000 to 5000 units per cubic centimeter produced a definite inhibitory effect on their rate and amount of growth. This effect was bacteriostatic in nature.

2. Bacillus alkaligenes fecalis however was found to be very sensitive to penicillin.

3. The activity of penicillin was progressively destroyed by the growth of these bacteria, particularly the Escherichia coli and Bacillus pyocyaneus in 4, 8, and 12 hours. The rate of destruction was greatest during the 8 to 12 hour period.

4. The degree of inactivation not only varied with the different types of bacteria but also with different strains of the same type.

5. The mechanical removal of devitalized tissue and purulent exudate followed by the topical application of higher concentrations of penicillin up to 1000 or 2000 units per cubic centimeter at frequent intervals of 8 hours or less is suggested in the local therapy of infected wounds to minimize the gram negative bacterial inactivation of penicillin.

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IRREDUCIBLE INTUSSUSCEPTION IN INFANTS

Report of Two Successful Primary Resections

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KENNETH W. WARREN, M.D., Boston, Massachusetts

SUCCESSFUL resection of the intestine for intussusception in infants under 1 year of age is rarely achieved. Dowd, in 1913, collected 8 cases of successful resection of the intussuscepted bowel in infants below this age. By 1921, Clubbe could find but 19 instances of intestinal resection performed for intussusception under 1 year in which survival occurred. Wangensteen, in 1942, reported a recovery in a 4 months old infant following a stage resection by exteriorization, and in the same communication he recorded the achievement, by Dennis, of a primary aseptic resection of the terminal ileum in an infant of 2 months. Alberts' successful case, a new-born infant, reported in 1941, had a primary resection with an open anastomosis. Recently, we have had occasion to resect a portion of the bowel in 2 infants with intussusception in which recovery ensued.

CASE 1. S. R., white female, 8 months of age, was admitted to the Henry Ford Hospital August 18, 1943, with regularly recurrent attacks of abdominal colic of 6 hours' duration. The pain was sudden in onset and extremely severe. With each paroxysm, the baby would assume an attitude of acute flexion and cry out vigorously. Between attacks the patient would sleep quietly and appear perfectly normal in every respect. The mother had given the infant an enema and secured three small blood clots in the returns. There had been no vomiting. Examination revealed the temperature, pulse and respirations to be normal. The patient was a well developed and well nourished white female infant of 8 months, alternately doubled up with pain and sleeping quietly. The skin was dry and cool. The remainder of the physical examination was normal except for the abdomen which was soft and not distended. Pain was elicited on deep pressure in the right upper and right lower quadrants and the baby turned to the prone position and flexed his legs when the abdomen was palpated deeply. A sausage shaped mass was felt repeatedly in the right side about the level of the umbilicus by some examiners and not at all by others. Rectal examination several hours after admission revealed the presence of blood and mucus on the examining finger. No masses could be felt per rectum. Operation was performed 16 hours after admission. The infant was anesthetized with open drop ether and the anterior abdominal wall was infiltrated with ½ per cent novocain solution in the right transrectus plane just above the level of the umbilicus. The abdomen was opened through a transverse incision. Exploration revealed a mass of intussuscepted bowel in the region of the transverse colon. The distal portion of the intussusception was reduced by manipulation within the abdominal cavity. The remaining mass was delivered through the incision and the ether anesthesia was arrested at this point. The ileocecal portion of the intussusception was reduced with moderate ease but the enteroenteric mass was irreducible. The involved segment of ileum was resected with end-to-end aseptic anastomosis. The incision was closed in layers with interrupted fine silk. Examination of the specimen revealed a Meckle's diverticulum, near the apex of the intussusception.

Continuous gastric suction was instituted and parenteral fluids, including blood, plasma, amino acids, glucose and saline were given freely. The early postoperative period was devoid of untoward incident, and a normal stool was passed on the fifth day. Two days later the abdomen became distended. The temperature rose to 102.8 degree F. and the infant appeared acutely ill. After a few troublesome days the ileus disappeared and the patient made rapid strides toward recovery. She was discharged September 2, 1943. Subsequent course has been uneventful.

CASE 2. C.H.No.390156. A 5 month old white male infant was awakened at 5:00 a. m. on March 3, 1944, screaming with abdominal pain which persisted 2 or 3 minutes and then relaxed spontaneously. The pain recurred at regular intervals and increased steadily in severity. Between paroxysms the baby relaxed and went to sleep. The patient vomited twice and passed one stool which contained some blood clots. The infant was brought to the hospital 6 hours after the onset of symptoms.

Examination revealed a well developed and well nourished male infant whose skin was pale and cool. Temperature was 98 degrees F. The abdomen was soft and rounded with an elongated mass in the right upper quadrant beneath the costal margin. Rectal examination revealed the presence of bloody mucus.

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The patient was given plasma and blood transfusions immediately and taken to the operating room. Open drop ether anesthesia was administered and the abdominal wall was infiltrated with ½ per cent novocain solution in the right transrectus plane just above the level of the umbilicus. The abdomen was opened through a transverse incision. The ether anesthesia was eliminated at this time, and the remainder of the operation was performed under local anesthesia. The apex of the intussusception had progressed from the terminal ileum to the splenic flexure of the colon. The distal portion of the intussusception reduced with ease and reduction continued uninterruptedly until the ileocecal valve was reached. The final stages of reduction was difficult but was finally accomplished without undue trauma to the bowel. The terminal ileum, cecum and terminal portion of the ascending colon were gangrenous. Thrombosis of the ileocolic vessels was observed. The t rminal 3 inches of the ileum, the cecum and proximal 1 inch of the ascending colon were removed, and an open side-to-side anastomosis was done between the ileum and ascending colon. The incision was closed in layers with interrupted fine silk. Postoperatively the patient was placed in an oxygen tent and given parenteral fluids including blood, plasma, glucose and saline. Continuous gastric suction was maintained for 4 days. The clinical course was relatively smooth until the seventh postoperative day when the temperature became elevated to 102 degrees F. Examination revealed moderate injection of the pharynx and injection of the tympanum membrane bilaterally. The fever continued at this level for 5 days and then subsided without further incident. Normal bowel activity returned on the second day after the operation and oral feedings were resumed on the fifth day. The patient was discharged March 22, 1944 and has pursued an uneventful course since that time.

The factors militating against the accomplishment of primary resection have seemed so numerous and so uncompromising that the procedure has been condemned by many surgeons who, because of their peculiar experience, are qualified to speak authoritatively on the subject. Unfortunately, the alternatives to resection with immediate restoration of continuity of the bowel in the presence of irreducibility and gangrene are associated with an equally forbidding mortality and are anatomically and physiologically less plausible.

FACTORS INFLUENCING RECOVERY

Significant factors which influence the course of intestinal resections in infants may be divided conveniently into 3 phases.

Preoperative phase. In the preoperative period the early recognition of the intussusception is of paramount importance. The classical description of the disease is usually reproduced with such fidelity that the diagnosis is rarely difficult. Delay on the part of the parents in bringing the infant to the physician accounts for the majority of late diagnoses, but occasionally the apparent benignancy of the condition and failure to feel the abdominal mass will lead the surgeon into grievous error.

Once the diagnosis has been established, surgery should be delayed no longer than is required to render adequate preoperative preparation. This preparation should comprehend the treatment of shock which is often present in some degree, and the restoration of fluid and electrolyte balance. Failure to observe this important aspect of preoperative therapy has, in our opinion, contributed in a real sense to the high mortality of intestinal resection in infants. The immediate administration of plasma, until properly typed blood is available, should be employed routinely and the infusion should be continued throughout the operation. This procedure, if carried out with dispatch, need not delay surgical intervention.

A nasal catheter should be passed in order to maintain the stomach in a state of decompression during and subsequent to the operation. There can be little doubt that infants tolerate intubation poorly, but we believe that the advantages outweigh the disadvantages even in patients of this age.

Operative phase. The important considerations bearing on the operative phase of treatment are numerous.

The anesthetic of choice is open drop ether, but the related factors of depth, duration, and supplemental agents deserve particular attention. Infants, already suffering from shock, submitting to a major surgical procedure which involves considerable manipulation of the abdominal viscera tolerate deep and prolonged anesthetic very poorly. Consequently, it has been our practice to administer light ether anesthesia, followed by liberal infiltration of the abdominal wall in the region of the proposed incision with a ½ per cent solution of novocain. The abdomen is opened and the portion of the intussusception which can be reduced easily is manipulated intra-abdominally.

The remaining mass is delivered through the incision and the mesentery is injected with the novocain solution. The general anesthetic is arrested at this point, and the remainder of the operation, including the resection and the closure of the abdominal wound, is accomplished under local anesthesia. The importance of this feature cannot, in our judgment, be overemphasized.

Despite the preponderance of expert opinion in favor of the right rectus incision we have employed a transverse approach just above the level of the umbilicus, cutting across the right rectus muscle. The exposure is entirely adequate, and there is a minimum of meddlesome protrusion of small intestines through the wound. The transverse incision is easier to close under local anesthesia than is a right rectus, and the former incision is less apt to result in postoperative disruption or subsequent herniation.

Postoperative phase. Following the operation these patients are treated as vigorously, and in the same manner, as if they had generalized peritonitis. Continuous oxygen therapy and continuous gastric suction are instituted immediately. Adequate fluids, including a small daily transfusion of whole blood, are given by the intravenous, subcutaneous, and transmedullary routes.

SUMMARY AND CONCLUSIONS

Primary resections for irreducible intussusception are reported in 2 infants aged 8 months and 5 months, respectively. Recovery ensued in both patients.

1. The successful resection with primary anastomosis of irreducible intussusception in 2 infants aged 8 months and 5 months respectively is recorded.

2. The factors influencing a favorable outcome were early diagnosis, adequate preoperative preparation, minimal amount of general anesthetic, and specialized postoperative care.

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THE SURGICAL ASPECT OF INTESTINAL AMEBIASIS

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NO surgeon can practice for long in the tropics without realizing that his work includes many conditions which at first might appear outside his province. It is often assumed that his responsibilities in intestinal amebiasis are confined to the treatment of complications such as abscess and perforation, but experience in endemic areas has shown that the disease constantly recurs in surgical practice in forms which demand a wide knowledge of this prevalent disease, while operations for these complications are comparatively rare. Similar problems may also arise at home in view of the return of so many troops who have been exposed to this infection. Intestinal amebiasis is noted for its tendency to relapse and for its long persistence, and, although there seems little danger of an outbreak in England (41), it is likely to appear in sporadic form for many years to come.

The object of this paper is to review the types of intestinal amebiasis which frequently arise in surgical practice in endemic areas; distant complications, such as hepatic abscess, are not included. It is based on experience gained during 4 years of hospital work in the tropics, and on a study of the literature, although the conditions of military service imposed unavoidable restrictions. The observations are supplemented with illustrative examples from a series of 450 cases of intestinal amebiasis, admitted to a British General Hospital in South India between July, 1942, and March, 1944.

PATHOLOGY

The following notes are intended as an introduction to the clinical discussion which forms the main part of the paper. Interest mainly centers on the amebic infections which involve a restricted portion of the bowel, on account of their resemblance to the lesions caused by surgical diseases. Clark's postmortem investigations on the incidence and distribution of the lesions of intestinal amebiasis are generally accepted. He found that ulcers were scattered throughout the large intestine in 61 per cent of the cases, while isolated areas were alone involved in 34 per cent, and in the following order of frequency: cecum, ascending colon, rectum, sigmoid, appendix, splenic flexure, and hepatic flexure. As is well known, the inflammatory reaction which follows infection by the Endamoeba histolytica may be acute or chronic, and of almost any degree of intensity; secondary infection plays a large part in the changes produced.

Acute infections. The cecum will be used for purpose of description as this is the commonest site to be affected, but similar changes may occur in any part of the large intestine.

In the mildest attacks the ulceration is so confined to the mucosa and submucosa, with little surrounding reaction; there may be no evidence of the underlying condition when the cecum is examined from the serous surface. When the attack is more severe the ulceration is accompanied by changes very similar to those of other acute infections; edema and congestion are found in the cecal wall, fibrin is deposited on the surface, and there is surrounding peritonitis. A reddened, granular thickening of the serous coat, of patchy distribution, is a common appearance. The effects are usually diffusely distributed, and not in excess in the vicinity of the appendix, but exceptions occur, and if the appendix is also involved, the condition may be indistinguishable from nonamebic acute appendicitis. Occasionally fulminating infections are seen, in which acute phlegmon of the cecum develops, frequently followed by gangrene, perforation, and peritonitis. Attacks of this intensity are usually fatal, but the less severe infections commonly subside without incident, although occasionally complicated by abscess or perforation.

Chronic infections. Certain varieties are of particular surgical interest.

From a British General Hospital.

The diffuse form. Chronic ulceration causes extensive thickening and fibrosis of all layers of the bowel. Multiple areas are affected, with a predilection for the cecum and sigmoid colon, and alternate with segments of attenuated intestinal wall. Occasionally the whole length of the large intestine is thickened.

The localized form is discussed under "amebic granuloma."

The solitary chronic ulcer most often occurs in the rectum. The size varies and may extend to several square inches. Exuberant vascular granulation tissue is found in the base, and the margins are thickened and edematous—appearances which may readily be mistaken for malignancy. The mucous membrane in the vicinity may be very edematous in the form of pseudo-polyps. Chronic amebic ulcers may very occasionally become malignant (27).

The fibrous stricture. Rogers considers that fibrous stricture rarely follows amebic infection (35), but this is not the experience of other observers (12, 24, 30). According to Lynch "When cicatrical deformity of the colon and extensive peritoneal fibrosis have resulted from prolonged or deep or extensive infection, the damage is more or less permanent even if the ameba is eradicated." Stricture is probably the result of associated secondary infection, for the Endamoeba histolytica induces little inflammatory reaction of itself (12). It is often surprising to see at sigmoidoscopy how even advanced amebic ulcers of longstanding resolve with little or no scarring. Applying the modern criteria for diagnosis, including biopsy, amebiasis is a rare cause of rectal stricture. It may be noted here that the identification of the Endamoeba histolytica in the tissues requires special experience, and in this type of lesion may present difficulty even to the expert.

Amebic granuloma or ameboma. Prolonged infection under certain conditions, as may occur in the delayed resolution of an acute infection, gives rise to an inflammatory thickening which gradually becomes defined to form a discrete mass—in the case of amebic infection this is known as amebic granuloma or ameboma. The cecum is most often affected, but ameboma may occur in the sigmoid and other parts of the colon. The omentum is usually adherent, and the appendix may be included in the mass, which may also involve the ascending colon and attain a considerable size. To the naked eye, the condition may suggest the results of acute appendicitis, diverticulitis, or regional ileitis. Chronic amebic ulceration occasionally produces an analogous condition in which fibrosis predominates. When a localized segment is affected, carcinoma, hypertrophic tuberculosis, or diverticulitis may be closely simulated (15, 18).

Amebiasis of the appendix. Amebic infection of the appendix arises by extension of the infection from the cecum, and whenever the cecum is extensively affected, the appendix is likely also to be involved. Most examples are subacute rather than acute. The incidence has been determined at postmortem examination of patients who died from amebic dysentery. In Clark's series of 186 postmortem examinations, the appendix was involved in 41 per cent, and 9.2 per cent abscess or perforation had occurred (8). His series is exceptional, for only a small proportion of the patients had received emetine. Craig found 16 examples in 60 necropsies, and Strong reported 7 in a series of 100.

The pathological changes range from pin point ulcers confined to the mucosa and submucosa, to inflammatory reaction which includes the whole organ. In the more severe infections, edema is a prominent feature; the walls are thickened, pus is found in the lumen, and the serosa is congested and may be covered with fibrin. Similar changes are usually found in the cecum. Abscess and perforation have been cited, but clinical experience indicates that these complications are rare if emetine is employed. Examination of the contents of the lumen usually discloses the Endamoeba histolytica. Apart from the presence of the ameba, neither macroscopic nor microscopic appearances can be distinguished from those of nonamebic appendicitis. Remarkably few examples are reported in the literature of the discovery of the Endamoeba histolytica in the tissues of appendices removed at operation, even though they have been present in the lumen (14, 18, 24), but they are often seen in postmortem specimens with coincident amebiasis of the cecum.

The majority of appendicular lesions which develop during an attack of acute cecal amebiasis are of this type, but, of course, nonamebic acute appendicitis may also occur.

Following an attack of acute cecal amebiasis, interval appendicectomy occasionally reveals gross changes in the form of constrictions and adhesions, and the appendix may contain pus with amebae. Evidence of chronic inflammation is often seen on microscopic examination, but how far the appearances can be attributed to the previous amebic infection is conjectural.

Local complications of intestinal amebiasis. Perforation is frequently found at postmortem examination in fatal cases of intestinal amebiasis. Strong reports 19 per cent, and Clark 10.7 per cent (8, 39). The commonest sites are the cecum, sigmoid, appendix, and rectum; multiple perforations may take place. As in other diseases, the lesion may be acute, subacute or chronic, and either intraperitoneal or extraperitoneal. Most perforations appear in association with fulminating attacks, but the condition may arise in attacks of acute and chronic dysentery of any severity. In the retroperitoneal variety, abscesses may form and track widely into the perirenal, subphrenic, and pelvic spaces (10, 24).

Brief mention only will be made of other local complications. Spontaneous hemorrhage of serious proportions is occasionally seen—3 of our patients required transfusion on this account. Handling of the bowel at operation may be followed by dangerous hemorrhage from amebic ulcers; the cecum is particularly prone to this complication (3).

Intussusception is rare, and no instance occurred in our series, although 2 examples were seen in Indian hospitals during the same period. Spontaneous reduction may occur, as in a case reported by Parry. Adhesions, bands and kinking of the bowel are common sequelae, and an occasional cause of intestinal obstruction (7).

CLINICAL ASPECTS AND DIAGNOSIS

The clinical manifestations are just as varied as the pathological. Atypical forms are common, and may so closely simulate almost any gastrointestinal disease, acute or chronic, that it is important to give every consideration to amebiasis in the differential diagnosis when dealing with patients who have lived in endemic areas. In spite of modern treatment, relapse is frequent, sometimes after a long interval of apparent good health, and permanent cure should not be assumed.

The clinical diagnosis must be supported by the recognition of the Endamoeba histolytica in the stools, or in specimens from the walls of sinuses or obtained at sigmoidoscopy, or in biopsy material. In assessing the significance of the presence of the vegetative form of the Endamoeba histolytica, the fact that amebiasis may coexist with other conditions should not be overlooked. Endamoeba histolytica cysts so often occur in the stools of individuals in whom there is no demonstrable sign of disease that of themselves they are of little diagnostic value.

A further check on the diagnosis is provided by observing the effects of treatment with emetine. If complete resolution is not obtained, the diagnosis must be considered further to exclude a coexisting lesion. Very occasionally intestinal amebiasis is resistant to this drug—most often in examples of long-standing infection, or when emetine has been previously employed. The drug should be used with caution on account of its cumulative effect, and the danger of toxic action on the myocardium and nervous system (31, 40). Used with due care, its value as a control of diagnosis is very considerable.

In chronic attacks, investigation of the stools is an important step in the diagnosis, but in acute attacks, when an urgent decision must be made, this would involve too much delay—one or two negative stools are of no significance. Acute surgical conditions must be excluded, and, in the remainder, a provisional diagnosis is made on clinical grounds, and subjected in due course to laboratory confirmation. Unless this is obtained before emetine is given, the chance of discovering the ameba will probably be lost, but in unusually severe attacks immediate treatment takes precedence, and the accuracy of the diagnosis is later made evident by the response to emetine.

Acute intestinal amebiasis perforation. As previously noted, the majority of perforations

occur during the course of an unusually severe attack of intestinal amebiasis; occasionally a chronic ulcer perforates in a patient with few or no previous symptoms. It is unnecessary to refer in any detail to the clinical features as they do not differ from those due to other perforations. Severe toxemia from the associated intestinal amebiasis may almost completely mask the clinical evidence of perforation, and it is not a very uncommon experience for an unsuspected perforation to come to light at postmortem examination. Arising from a subacute perforation, an abscess may develop very insidiously and lead to difficulty in diagnosis, especially when the history does not suggest intestinal amebiasis; perirenal collections, for example, may be mistaken for typhoid, malaria, empyema, and hepatitis (31).

The incidence of clinical perforation is low; Strong reported 3 examples in 200 cases. In our series of 450 cases, there was only one perforation, which followed exploratory operation in a patient who died from a fulminating infection of the cecum and ascending colon (see Case M. H. following). In the following 100 cases 2 perforations occurred, 1 in the cecum in a patient moribund from a diffuse intestinal amebiasis, and the second in a very severe acute infection of the sigmoid, which proved fatal despite operation.

When perforation takes place in the course of fulminating attacks, the bowel is usually so friable that repair is problematical, multiple perforations may be found, and the toxemia is often overwhelming; the outlook even with surgical interference is very grave indeed. By contrast, in chronic and relapsing amebiasis, the condition of the bowel is much more favorable, and if emetine is not delayed, the prognosis approaches that of perforation due to causes (1, 11, 19).

Acute cecal amebiasis. Although there are certain individual features, acute cecal amebiasis may be accepted as representative of the localized acute forms of intestinal amebiasis which may affect any part of the large intestine.

When the infection is confined to the cecum, the consequences differ from those of the ordinary diffuse form, amebic dysentery, in many important respects: (a) pain is referred to the umbilical region, and not to the hypogastrium, (b) the local signs and local pain are confined to the right iliac fossa, (c) diarrhea, blood, and mucus, are less frequent, and not infrequently absent, and (d) in general it is more difficult to find the ameba in the stools. This particular difficulty must be recognized or the diagnosis may be overlooked, as occurred in some of the published cases (18, 23). Fortunately the response to emetine provides a convenient indication in suspected cases.

For the clinical discussion, 3 types of case will be considered: the fulminating, the acute, and the special variety, the acute cecal ameboma. All have certain features in common, which are presented in Table I.

Fulminating attacks are uncommon; the majority are severe from the start, but they may arise as an exacerbation of an ordinary mild intestinal amebiasis. The onset is rapid, and abdominal pain, both midabdominal and in the right lower quadrant, vomiting, pyrexia, and tachycardia are the prominent features, although subject to some variation. Diarrhea may appear either early or late, and it is followed by the passage of blood and mucus. The signs of local peritonitis appear early, and many patients fail to respond to medical treatment and succumb within a few days to the effects of gangrene or perforation.

A surgical opinion may be required in the less typical attacks. The onset is less abrupt, the toxemia more prominent, and the local signs remain more localized in the early stages than in the case of perforation, but, of course, when perforation complicates this type of cecal amebiasis, the diagnosis becomes formidable. Appendicitis can be excluded by the toxemia, the wide extent of the local signs in the early stages, and the departure from its typical mode of onset and course (Table I). If the diagnosis remains in doubt, laparotomy becomes obligatory.

The following case is presented as a fairly typical example:

M. H., aged 29 years, was admitted on August 6, 1942, complaining of diarrhea, with blood and mucus, and griping hypogastric pain for 4 days. This was his first attack. His temperature was 99 degrees, pulse rate 64, and respiratory rate 20 per minute. He was not dehydrated, and there were no localizing signs in the abdomen. The stools revealed an indefi-

nite exudate with blood, but no amebae or cysts, and a culture was made.

After 24 hours, severe and continuous pain appeared in the right iliac fossa, with nausea. Diarrhea was troublesome, and his temperature was 100 degrees, pulse rate 130, and respiratory rate 22 per minute. The tongue was furred, and marked tenderness and rigidity were found in the painful area, maximal at McBurney's point. No lump was found, and the psoas and thigh rotation tests and rectal examination were negative. To exclude perforation or appendicitis, exploration was advised.

At operation, local peritonitis with turbid free fluid, and an edematous and congested cecum, were disclosed. The appendix was in a similar state, and fibrin deposit was seen on both organs. Perforation and gangrene were excluded, and the operation was concluded with the removal of the appendix, which was very swollen throughout, and the contents were mucopurulent, but there was no perforation, gangrene or ulceration.

The next day saw little change in his condition, and he was still passing frequent loose, blood stained stools, apparently free from amebae. The culture of the early stool did not reveal any pathogenic organism. Later, his condition became increasingly serious. Although the diarrhea continued, and the stools were frequently examined, it was not until August 15 that the Endamoeba histolytica was found, and then in large numbers. Emetine was given to supplement his sulfonamide treatment, but without effect. On August 18, his blood count showed red blood cells—3.5 millions, hemoglobin 90 per cent, white blood cells, 7000. Many degenerate polymorphonuclear cells were present, and some myelocytes and nucleated red cells. A blood transfusion was given, but the patient died on the next day.

Postmortem examination disclosed a plastic peritonitis with widespread recent adhesions. Free pus was found in the right iliac fossa and in the right paracolic gutter extending upward toward the kidney. Pus was also seen behind the cecum. The appendix stump was sound, but a perforation had occurred in the posterior surface of the ascending colon. The cecum presented several patches of gangrene, and the whole of the large intestine was soft and friable, with extensive gangrene of the mucous membrane and amebic ulceration. The acute inflammatory process extended upward for 2 inches into the ileum.

This patient was admitted before our laboratory was opened, and histological examinations were not made. Commenting on the case in the light of subsequent experience of amebiasis, the cecum was noted at operation to be much more affected than occurs in appendicitis, and the possibility of amebiasis might have been confirmed by immediate examination of smears from the contents of the appendix. The lapse of several days before the endameba appeared in the stools is of interest—this also occurred in several of the recorded cases. We would now advise the empirical use of emetine immediately after operation in this type of case, rather than await a positive stool report. Involvement of the ileum has been found in only about 5 per cent of fatal cases of intestinal amebiasis.

The acute type of cecal amebiasis is much commoner than the type just described. Constitutional disturbance is slight, nausea and vomiting unusual, diarrhea rarely prominent, and abdominal pain is not excessive. The local signs tend to be disproportionally well marked. Complications are infrequent, and a response to emetine is to be expected within 3 days. Further details appear in Table I.

Involvement of the appendix by extension from the cecum is probably of frequent occurrence, as already noted in the remarks on pathology. From the clinical point of view, this extension is of little consequence, because both cecal amebiasis and amebic appendicitis are essentially medical diseases, clinically indistinguishable, usually responsive to medical treatment, and unsuitable for surgery unless complicated by abscess or perforation (12). Exceptional attacks do not react to emetine, as in the following example:

A. J., aged 24 years, was admitted on September 9, 1942, suffering from dysentery, which had commenced 6 weeks previously in the form of a mild diarrhea, later replaced by very frequent stools, with blood and mucus. This was his first attack. When examined, he complained of intermittent pains in both iliac regions, but apart from tenderness there no abnormality was found. The stools contained Endamoeba histolytica, and emetine and carbasone were given. Although the diarrhea was relieved, and the amebae disappeared from the stools, intermittent pains occurred, now in the umbilical and right iliac regions. The attacks took place three or four times a day, lasting for an hour or so at a time. The appetite was poor, but there was no nausea or vomiting.

The attacks increased in severity, and well marked tenderness developed in the right iliac fossa, and to a much lesser degree persisted in the left side over the sigmoid and descending colon. There was no rigidity and no mass. Repeated stool examinations were negative, and two sigmoidoscopies also showed no abnormality. On October 31 he had an attack of greater severity than before, and operation was advised.

Laparotomy revealed an edematous, injected appendix, with soft thick walls, and the adjacent

TABLE I.—CLINICAL FEATURES OF ACUTE CECAL AMEBIASIS AND DIAGNOSIS FROM ACUTE APPENDICITIS

Acute Cecal Amebiasis	Acute Appendicitis
Previous history	
Often previous attacks of dysentery. Commonly prodromal symptoms—anorexia, abdominal discomfort, vague ill health, mild diarrhea, or constipation.	Occasionally attacks of ? appendicitis prior to exposure to dysentery. Previous history of dysentery does not exclude appendicitis. No prodromal symptoms.
Onset	
May be sudden, commonly more gradual. Pain, referred or local, is usual presenting symptom, but attack may commence with diarrhea, or, in exceptionally severe attacks with vomiting and fever.	Sudden. Pain, almost always referred, is presenting symptom.
Pain—Referred	
Midabdominal, but also hypogastric if distal colon involved. Rarely severe. Usually colicky, occasionally aching. Intermittent with periods of partial or complete relief. Presenting symptom in about 50 per cent of attacks. May only appear later, or remain absent.	Umbilical or epigastric. Colicky or aching. Frequently severe, and constantly recurring or continuous. Typically the presenting symptom.
Pain—Local	
Present in right iliac fossa from earliest stage of attack, or as initial symptom. Tends to be diffuse from the first. Also occurs over distal colon and liver, if involved. Usually an ache of moderate intensity.	In vicinity of appendix. Appears some time after referred pain. Very occasionally the initial symptom. Well localized at first, extending later. May be severe.
Nausea and Vomiting	
Both absent in mild attacks, but to be expected in very severe attacks.	One or both generally occur.
Diarrhea	
Appears early in rather less than 50 per cent of attacks, and may be initial symptom. May appear after some days. Usually not severe. Blood and mucus also inconstant. Occasionally constipation. If distal colon also affected diarrhea more likely.	Constipation usual. Occasionally diarrhea is an early symptom. With pelvic abscess; blood and mucus may be passed.
Endamoeba histolytica in stools	
Vegetative Endamoeba histolytica usually but occasionally not found, even with repeated examinations of stools. Commonly only found after some days.	Presence of Endamoeba histolytica does not exclude nonamebic appendicitis.
Constitutional disturbance	
In milder attacks notably less marked than the intensity of local physical signs would suggest. Slight rise of temperature and pulse from onset. In exceptionally severe attacks high fever, tachycardia, and dry furred tongue.	Moderate rise of temperature and pulse from a few hours after onset of attack. Constitutional effects keep pace with local physical signs. Tongue increasingly furred. Pyrexia and tachycardia not features of early acute appendicular obstruction.
Tenderness and rigidity	
Tenderness usually moderate, may be acute. Typically diffuse in right iliac fossa from very early in attack. Also over distal colon and liver, if involved. Rigidity is typically diffuse and incomplete, and does not mask thickened cecum; occasionally rigidity is well marked.	Tenderness appears some time after original pain, usually acute. Localized at first over appendix, later extending, but not in line of colon. Rigidity localized at first, later extending, often pronounced and preventing palpation of abdominal contents.
Palpable mass	
Thickening of cecum apparent early, and, if resolution is delayed, gradually becoming more defined. Tender at first, less so later. May persist for considerable time if emetine is omitted. Abscess formation uncommon.	Appears late, and slowly subsides or forms abscess.
Special signs	
Psoas sign, thigh rotation sign, and hyperesthesia rare; Rovsing's sign, rebound tenderness common. Rectal tenderness rare.	Psoas sign, thigh rotation sign, and rectal tenderness common in certain positions of appendix. Hyperesthesia, rebound tenderness, and Rovsing's sign often present.

TABLE I.—CLINICAL FEATURES OF ACUTE CECAL AMEBIASIS AND DIAGNOSIS FROM ACUTE APPENDICITIS—Continued

Acute Cecal Amebiasis	Acute Appendicitis
Leucocytosis	
Depends on severity of attack. Moderate rise with relative reduction of neutrophils common. High counts of 20,000+ may occur in very severe attacks, but quite inconstant. In ameboma slight rise in the more acute phases. The changes in the blood count are not invariable, but when present afford useful confirmation.	In inflammatory type of appendicitis rise to moderate level some hours after onset. Neutrophils increased disproportionately. Not a feature of obstructive appendicitis. Leucocytosis with neutrophil excess to be expected with abscess.
March of symptoms	
Order of appearance of symptoms subject to considerable variation. Abdominal pain, referred or local, usually first symptom.	Remarkably constant onset and sequence of events commencing with pain.
Effect of emetine	
Typically clinical response in 2 or 3 days, but exceptions.	Nil.
Sigmoidoscopy	
In attacks clinically confined to the cecum, positive findings in about 10 per cent.	Negative unless coexisting dysentery.

cecum presented a roughened and injected surface. There was no free fluid, and exploration disclosed no further pathology. On removal, the appendix contained mucopus, and the mucosa was very swollen and showed numerous small areas of hemorrhage although trauma from handling had been reduced to a minimum. The caliber of the lumen was much reduced by the edema. Microscopic examination of the contents showed pus cells, red blood cells, and numerous Endameba histolytica. The histology revealed congestion of the small vessels, shallow ulceration of the mucosa, and in and beneath the mucosa, masses of nongranular leucocytes and eosinophils. The eosinophil cells comprised about 1/10 of the total cells observed. Although structures bearing some resemblance to Endamoeba histolytica were seen in and beneath the mucosa, their identity was not established when an iron hematoxylin stain was used.

Further emetine and carbasone were given. Convalescence was not entirely satisfactory; on the 7th day he complained of pain over the liver, which was found to be moderately enlarged. This attack soon subsided, but for about 3 weeks he complained of intermittent colicky pains in the midabdomen. Frequent stool examination and further sigmoidoscopy showed no abnormality. He was symptomless when he was sent for convalescence on December 12.

This appears to have been an example of amebic appendicitis, even though the Endamoeba histolytica was not found in the actual tissues. Although examinations of the stools and sigmoidoscopy repeatedly proved negative, evidence of amebiasis of both cecum and appendix was found at operation.

The third condition for discussion with acute cecal amebiasis is the acute cecal ameboma, which is occasionally found when resolution of an acute attack of cecal amebiasis is delayed, and is more likely to develop if emetine is omitted. In the early stages, tenderness and rigidity tend to obscure the mass; later, when the tenderness is less and the rigidity disappears, it is more easily defined. The temperature and pulse are little affected, and even in the presence of a large mass, which may involve the ascending colon, the constitutional disturbance is rarely severe. Exacerbations are not uncommon, and are accompanied by an increase in the local signs, and a moderate rise of temperature and pulse. A slight rise in the leucocyte count, of the type noted in Table I is usual.

However suggestive an abdominal mass may appear of appendicitis in patients who have lived in endemic areas, before operation is advised investigation should be undertaken to exclude amebiasis. In our experience sigmoidoscopy is not often helpful in this condition, and repeated examination of the stools quite commonly proves negative. The response to emetine is very much more constant, but, if this fails, laparotomy will be required for diagnosis. The following case of ameboma presented some interesting features:

In September, 1942, D. J., aged 30 years, was treated with emetine, grains 12, and sulfonamides for a mixed infection of amebic and Sonne dysentery. He was admitted to hospital on December 8, 1942, because of further diarrhea. Endamoeba histolytica

was found in the stools, and emetine and carbasone were given with complete relief of symptoms. On January 6, amebic ulcers of the rectum, confirmed by examination of the discharge, were found at sigmoidoscopy. Quinoxyl was given, both orally and by the rectum, but, although the diarrhea did not recur, a serious deterioration in his general condition set in, for which detailed investigation failed to find a cause. On February 6 he complained of pain in the cecal area, and a mass was discovered. A surgical opinion was obtained to exclude appendicitis. The swelling was tender and fixed, and about the size of a closed fist, but there was no rigidity. He was also slightly tender in the left iliac fossa, and there was a slight rise in temperature and pulse. Otherwise investigation, including blood counts, was negative, and the diagnosis of ameboma was accepted.

During the next week the temperature and pulse failed to settle and there was no change in his condition, except for the appearance of a minor degree of rigidity and some increase in the lump. On February 12 emetine was resumed; a week later a very remarkable reduction had occurred in the mass, although diarrhea, with blood and amebae had returned. Quinoxyl and carbasone were prescribed, and a gradual improvement in general condition followed. By the end of February, there was no sign of cecal thickening. During March he had more abdominal pain, again with diarrhea and amebae in the stools. A final course of emetine, carbasone, and quinoxyl was commenced on March 18, and, when he was transferred to another hospital on April 19 for return home, his general condition was much improved.

Relapse after emetine, even when supplemented with other drugs, is not uncommon. Emetine bismuth iodide was not available at the time, and it was only after every consideration that the physicians prescribed emetine to the extent of a total of 41 grains. Serious constitutional disturbance is unusual with ameboma, and it is probable that some other agent was responsible in this case.

The diagnosis of acute cecal amebiasis from appendicitis. More than 30 years ago Rogers (35) described cecal thickenings, in cases of amebic dysentery, which simulated appendicitis, and which he "had seen mistaken by physicians and surgeons and in which the appendix proved not to be involved." Many surgeons have been interested in this problem, and there is ample evidence to support the view that "surgeons who work in tropical countries have found that they must be constantly on their guard to avoid operation in cases of amebic dysentery under the diagnosis of appendicitis" (6, 11, 23). Even in temperate climates the same difficulty may arise, as was witnessed during the Chicago epidemic of 1933—1934, when, of 1,215 cases of amebic dysentery, 32 were diagnosed as appendicitis and submitted to operation.

In the remarks which follow, no special reference will be made to amebic appendicitis, as this is merely an extension of the infection from the cecum. The immediate diagnosis of acute cecal amebiasis is essentially clinical, and laboratory confirmation must come later. As a general rule there is little difficulty in diagnosis —especially when there is evidence of involvement of the more distal colon or liver. When the disease is confined to the cecum, the distinction becomes finer, and occasionally the disease so closely simulates appendicitis that recognition is not possible by the clinical methods at our disposal. Surgeons necessarily meet a high proportion of the more difficult cases, but on account of the special risks of operation on the amebic abdomen, every effort should be made to arrive at a diagnosis without resort to laparotomy, although this must be advised if there is serious doubt.

The individual items of diagnosis are presented in Table I, but a few general observations will be added.

The manifestations of acute cecal amebiasis are much less constant than those of appendicitis, and, even when there is considerable resemblance, it is usually possible to recognize some essential feature which cannot be integrated into the typical pattern of appendicitis. On the other hand, the unexpected irregular attack of appendicitis is, in the tropics, very liable to be mistaken for dysentery, especially if the typical history is lacking. In the high retrocecal position with comparatively mild symptoms appendicitis may suggest amebiasis of the cecum, or, in the pelvic position with hypogastric pain it may lead to a suspicion of dysentery affecting the distal colon. Acute appendicitis associated with diarrhea is, of course, a well known trap.

In distinguishing these conditions in which the clinical features may be so similar, success often depends on details—details of the previous history, of any premonitory symptoms, of the onset and progress of the attack, and of

the individual signs and symptoms. Rayner's observation "the old dictum 'quick in and quicker out' has long since been obsolete; always there is time to make a considered diagnosis as there is to do a careful and gentle operation" (34) is even more applicable to the diagnosis of appendicitis in the tropics than in temperate climates, and, in any case of suspected appendicitis, amebiasis must always be excluded.

The local signs of acute cecal amebiasis commonly appear earlier, and are at first more diffuse than those of appendicitis, but they are by no means constant, and not infrequently appear most suggestive of acute appendicitis. A common error is to exaggerate the importance of the local physical signs while neglecting the general aspects of the case; we have seen many examples of amebiasis diagnosed as appendicitis on this account. Failure to appreciate that the onset of an attack of cecal amebiasis may be very abrupt, and that diarrhea is frequently absent during the first few days are other causes of misdiagnosis.

As already noted, the individual signs and symptoms in amebiasis are much less constant than those of acute appendicitis; this inconstancy applies also to the order of their appearance. In acute appendicitis exceptions to the rule "First and all the time the pain, next nausea, then tenderness, and finally fever with leucocytosis" are remarkably rare (9, 20) but in acute cecal amebiasis no set order applies.

Occasionally acute abdominal signs develop during the course of an attack of amebic dysentery and center in the right iliac fossa. The differential diagnosis then includes (a) an exacerbation of cecal amebiasis, with or without extension to the appendix, (b) nonamebic acute appendicitis, and (c) perforation of an amebic ulcer. The diagnosis of perforation will not be considered further. The evidence may be sufficient to enable a definite diagnosis to be made in the more severe attacks of nonamebic appendicitis, especially of the obstructive variety, or at least to leave no doubt about the necessity for exploration. More often it is less convincing, and a frequent result of exploration under these conditions has been the discovery of acute amebiasis of the cecum, and at times also of the appendix, but not a *surgical* appendicitis (12). In the clinically less severe attacks, any bias should be in the direction of amebiasis.

The indications for operation in the "doubtful" case. When the diagnosis remains in doubt, two considerations must be weighed in the balance: the dangers of postponing operation in acute appendicitis, and the special risks of operation in intestinal amebiasis. (The reader is referred to the section "Operations in Relation to Intestinal Amebiasis" which follows.) The danger of delay in appendicitis needs no comment, and examples of apparently mild attacks which at operation prove to be much more serious are by no means rare. Nevertheless, when amebiasis is the alternative diagnosis, with the attendant risks from operation, a conservative attitude may well be the safer policy if all the clinical evidence points to a mild attack.

If a severe attack of appendicitis cannot be excluded with reasonable certainty, exploration must be advised. For the obviously mild attack, and the attack which appears to be settling down, conservative measures, with emetine, should be given a trial. When acute symptoms develop during an attack of amebic dysentery, exploration is indicated if the attack is clinically severe, but with less severe symptoms the bias should be against operation. When there is a localized mass in the right iliac fossa, whether the cause is ameboma or acute appendicitis, there is no indication for immediate interference; the attack should be treated conservatively, with emetine. Operation is required only if an abscess develops, or if the mass persists, when it becomes necessary to exclude such lesions as tuberculosis, ileitis, and carcinoma.

In perspective. Attention has been focused on acute cecal amebiasis and its diagnosis from acute appendicitis. Amebic infections may, of course, localize in other parts of the large intestine with effects analogous to those described. The possibility of other important diseases which may present a similar clinical picture must not be overlooked. These include malaria, hepatitis, both amebic and infective, typhoid, cholecystitis, ulcerative colitis, and some forms of bacillary dysentery; all may give rise to acute abdominal symptoms

which may concentrate in the lower right quadrant of the abdomen. Their salient features are well known and will not be described.

CHRONIC INTESTINAL AMEBIASIS

Amebiasis and "chronic" appendicitis. The high incidence of amebiasis among soldiers serving overseas, and its tendency to persist for long periods and to relapse, make this subject exceptionally important. After the war postdysenteric abdominal disorders will undoubtedly appear frequently in general surgical practice. For purpose of discussion, patients may be divided into two groups: (a) those who have lived in endemic areas, but give no history of infection, and (b) those who have had intestinal amebiasis.

In the first group, the possibility of unsuspected intestinal amebiasis as a cause of the symptoms must not be overlooked. However suggestive the case may be of appendicular disease, operation is not to be advised until amebiasis has been excluded by adequate investigation. Clinical features which suggest amebiasis are: a characteristic, diffuse, rather tender thickening of the cecum, a tender, firm, sigmoid colon, and tenderness or enlargement of the liver. Tenderness and thickening is sometimes present over other parts of the colon. Investigation will include frequently repeated examination of the stools, sigmoidoscopy, and x-ray examination—this may reveal unsuspected disease in the colon. If, after complete investigation, there is no evidence of amebiasis, operation will be advised on ordinary surgical principles.

In the second group of patients, symptoms are often too readily assumed to be the result of chronic inflammatory changes in the appendix, caused by the attack of dysentery, for which operation is necessary. It is important to remember that the patient, having already had dysentery, is liable to relapse, or may have been reinfected, and symptoms which are very suggestive of appendicitis may be produced. In addition, however, the possibility of postdysenteric intestinal symptoms of nonappendicular origin must be considered. Such symptoms may be due to a neurosis, or to functional disturbances of the bowel, or to organic changes such as scarring and adhesions, attributable to the previous dysentery. Dyspepsia, anorexia, abdominal discomfort, irregularity of the bowels, and pain and tenderness in the right iliac fossa may be very suggestive of appendicular disease, but more often result from one of the other conditions. Even if the appendix is at fault, the lesion may be an amebic appendicitis which may well respond to medical treatment. Moreover, many patients, given time, recover spontaneously. For patients who fall into this group, if there is a history of recent dysentery, observation for some months is advisable before operation is resorted to, and in all cases the question of a trial of emetine or other amebicide should be considered by a physician.

Banerji and Chopra recommend an interval operation for every case in which the appendix appears to be acutely involved during the course of an attack of cecal amebiasis. They state that "patients are liable to subsequent attacks of appendicitis either as a result of chronic inflammatory changes in the appendix, or a recurrence of amebic lesions in the appendix." It is not unusual to find gross changes, of the type noted in the section on pathology, in appendices removed at interval operation, but we would recommend operation for amebic appendicitis only when every effort to cure the condition by medical measures has failed—unless, of course, some complication intervened. At present interval operation, following acute cecal amebiasis, is usually reserved for cases in which evidence of appendicitis persists after apparent cure of the cecal amebiasis. There is need for further investigation on this point because Banerji and Chopra base their opinion on an extensive experience.

Finally, attention is directed to the unsatisfactory results which follow indiscriminate appendicectomy in endemic regions. Rogers disclosed that a considerable number of chronic dysenteric patients were found by the India office to have had their appendices removed without lasting benefit (36). If a repetition of this experience is to be avoided, appendicectomy must be reserved for carefully selected patients.

Localized chronic amebic lesions of the cecum and colon. The diffuse form of amebic colitis,

which may simulate chronic appendicitis, cholecystitis, and duodenal ulcers, is well known, but the localized lesion, with solitary or multiple ulcers, thickening of the bowel, and often a palpable mass, has received little attention in general surgery. It is a rare lesion and the counterpart of the ameboma which occurs in the acute state, and, like it, is of surgical interest chiefly because it is so liable to be mistaken for a surgical condition. Occasionally, the disease causes an obstruction which requires operation. Typical cases have been described in the literature (15, 18, 32,37, 43), and the difficulties of diagnosis and the dangers attendant on operation in unsuspected cases are well described. These dangers were clearly revealed during the Chicago epidemic, and, no doubt, the publicity which followed ensured their wider recognition. However, the time has not yet arrived when a majority of surgeons would subscribe to Simon's experience: "whereas the previous tendency was to overlook amebiasis and to diagnose carcinoma or tuberculosis, now the tendency is in the opposite direction."

The clinical features require no elaboration, and will be referred to in general terms only, in order to emphasize their close similarity to those of other granulomas and neoplasms of the bowel. In all, the effects depend on the portion of the intestine involved, the extent of the ulceration, and the degree of mechanical obstruction. As is well known, while in lesions of the lower part of the colon alternating diarrhea and constipation, and the passage of blood and mucus, are usual, in the midcolon obstructive symptoms are likely to predominate. In the proximal colon, especially in the cecum, a mass of considerable size may develop silently, as far as bowel symptoms are concerned, although reflex gastrointestinal symptoms may occur. Palpation may reveal the presence of a mass, and radiological examination will define its position and extent. A history of previous dysentery would merely indicate the necessity of special investigation.

It is generally agreed that radiological appearances are not pathognomonic of this condition. Deformities of the cecum, due to contraction and induration, such as a "coned" appearance have been described but they are neither constant nor distinctive (27). Deformity of the colon, from ulceration or fibrosis, may be marked, but cannot be distinguished with certainty from other inflammatory or malignant conditions. Extensive deformity would support the diagnosis of amebiasis, but Ikeda's opinion, that the chief value of radiology is the diagnosis of the site and extent of these lesions and as a control of treatment, represents the limitations of the method.

Differential diagnosis from carcinoma, tuberculosis, diverticulitis, and rarer conditions such as regional ileitis, actinomycosis, and chronic bacillary lesions, involves the accepted clinical, radiological, and laboratory investigations, and may provide conclusive evidence of one or other of these diseases. In this variety of amebiasis, neither clinical nor radiological features are distinctive, and diagnosis depends on the discovery of the ameba and the diagnostic use of emetine.

The detection of the Endamoeba histolytica in the stools may prove difficult, and the greatest importance is attached to the details to be observed in the selection of specimens for examination and the immediate examination of fresh specimens on several successive days (25). Sigmoidoscopy may succeed when the stool tests fail, but, as would be expected, the percentage of positive results will be small when the proximal colon is affected. Finally, emetine should always be employed for the diagnosis of "tumors" of the large intestine in patients who have lived in endemic areas, whether the Endamoeba histolytica has been isolated or not. The effect should be assessed not only by clinical laboratory, and radiological examinations, but also, when applicable, by sigmoidoscopy. Most amebic lesions respond conclusively, but in some of the fibrous forms emetine has little effect. In view of the possible coexistence of other lesions, if complete resolution is not obtained, biopsy or excision then becomes necessary.

Two cases will be described to illustrate some of the points raised:

M. E., an officer's wife, aged 32 years, was seen in consultation as an out-patient on November 7, 1942. She complained of pain in the right iliac fossa, off and on for about 2 months, and of occasional mild fever and some loss of weight. Her appendix had

been removed when she was 18 years old, and at 27 she had amebic dysentery. She had recently been investigated in another hospital, where a mass was discovered in the cecal area. The stools were negative, and x-ray showed an irregularity of the cecum and some delay in emptying of the ileum. She had been advised to have a laparotomy on the provisional diagnosis of tuberculosis. On examination there was found a slightly tender mass, corresponding in size and position with the cecum, as seen in the x-ray picture; no other abnormality was noted. She was advised to have further investigation before submitting to operation, but, while awaiting admission, she developed another attack of amebic dysentery. Six weeks later, after routine treatment, her weight had increased, her abdominal symptoms were almost completely relieved, and there was no sign of the mass previously present in the right iliac fossa.

L. H., aged 25 years, was admitted on February 13, 1944, with diarrhea and vomiting of about 12 hours' duration. He had suffered from intermittent attacks of diarrhea, flatulence and colic for about 3 months and considerable loss of weight.

Bacillary dysentery was at first suspected, but sulfonamides only brought partial relief of the diarrhea, and the stools continued to show blood and at times an inflammatory exudate, but no amebae. An ill defined mass was found in the right hypochondrium, below the liver. Further stool examinations resulted in the discovery of Endamoeba histolytica, both vegetative and cystic, on February 23. After 12 grains of emetine his general condition was considerably improved, and the diarrhea was completely relieved, but the mass remained unaffected. An x-ray examination on March 19 showed a constant filling defect, of the ring type, in the right half of the transverse colon. Repeated examination of the stools and sigmoidoscopy produced no evidence of amebiasis.

At operation on March 28 for suspected carcinoma a wide resection of the terminal ileum, cecum, and colon was performed for a tumor in the site indicated by x-ray film. The mesocolic glands were moderately enlarged, but there was no sign of hepatic or other metastases. The remaining ends of the ileum and colon were used to provide a colostomy.

The specimen presented a typical carcinomatous ulcer, almost encircling the bowel, and three small ulcers of the stercoral type. Scrapings from these ulcers failed to show amebae, and microscopic examination of the large ulcer showed columnar celled carcinoma, with inflammatory changes only in the glands. Convalescence was uneventful, and 6 weeks later the colostomy was successfully closed.

AMEBIASIS OF THE RECTUM AND ANAL CANAL

Amebiasis of the rectum and anal canal will be considered in two parts: amebiasis in relation to simple conditions, such as piles, fissure, fistula, and fibrous stricture, and amebic conditions simulating neoplasm.

The piles, both internal and external, which so commonly accompany an attack of amebic dysentery, usually resolve as the dysentery is brought under control, although in exceptional cases operation is required at a later date. Prolapse acts in a similar manner. Piles due to mild or chronic dysentery are of greater surgical importance, for the dysentery may be far from obvious and operation may be advised (17). Such cases are potential surgical catastrophes, and interference may be followed by an acute exacerbation of the dysentery—a most unwelcome sequel to a rectal operation—and by severe local complications, and even by liver abscess. McCoy reports that 6 patients suffering from dysentery during the Chicago epidemic were submitted to operation for piles, one of whom died.

In our experience in an endemic area, among the patients referred to hospital for the treatment of piles and fissures, many were found to have amebic dysentery or amebic proctitis. There was often no history to suggest dysentery, and some patients had been "cured" of this condition in the past. Proctoscopic examination alone is not sufficient, and sigmoidoscopy and repeated stool examinations may be required to bring to light the less obvious amebic infections. It is thought that postoperative troubles, such as ulceration and scarring, which appear to be more liable to occur in the tropics than in temperate climates are often caused by unsuspected dysentery.

Among the less common complications of amebiasis are conditions such as fistula-in-ano, anorectal abscess, and perianal ulceration. It is often not possible to find the ameba in the discharge, but examination of scrapings from the walls of the cavity is more successful. Biopsy may be used to establish the diagnosis, although in most cases spectacular confirmation is provided by the response to emetine.

Jackman noted the low incidence of fistula and anorectal abscess in this disease, and contrasted his figure of 1.7 per cent with the 30 per cent he found in cases of regional ileitis, and 8.4 per cent in ulcerative colitis. Two instances of fistula-in-ano occurred in our series. Extensive perianal ulceration was commonplace before the introduction of modern treatment, but is rarely seen today, and on

that account the diagnosis may be missed in chronic cases. Gabriel described a remarkable example in which widespread amebic ulceration followed the rupture of an anal abscess in a patient who gave no history of dysentery; the condition responded to emetine. One of our patients, seriously ill with longstanding amebic dysentery, developed an extensive perianal ulceration with much overgrowth of granulation tissue, which was very suggestive of condylomas in appearance. The Wassermann reaction was negative, and the condition ultimately resolved completely, without contraction, on treatment with emetine, carbasone, quinoxyl, and simple local applications.

The following cases are of relevant interest:

J. T., aged 35 years, was admitted for operation for piles on September 22, 1942. There was no history of dysentery, and, apart from a mass of interoexternal piles, proctoscopy showed no abnormality. The operation of excision and ligation was performed, and progress was satisfactory until the end of the second week, when he complained of pain in the right shoulder and right hypochondrium. The operation area was almost healed, but the liver was tender and a remittent pyrexia, without rigors, followed. Blood counts showed a leucocytosis with slight excess of polymorphonuclears, and serial x-ray pictures revealed progressive elevation of the right dome of the diaphragm. Treatment with emetine was given, without clinical improvement. Aspiration was carried out, and thick pus was evacuated; this was sterile and showed degenerated pus cells and amorphous débris. The patient was gravely ill and losing ground, and on October 16 and 20 operation was performed in two stages for subphrenic abscess. Later examinations of the discharge resulted in finding numerous Endamoeba histolytica and further emetine was given. Apart from the necessity of treatment for syphilis further convalescence was uneventful. Repeated examination of the stools failed to isolate the endameba.

This patient was admitted before repeated examinations of the stools and sigmoidoscopy were adopted as a routine preoperative measure in cases of piles, although it may be noted that, after operation and before emetine was given, the stools were negative.

Nevertheless it seems probable that the abscess was related to his operation.

J. F. D., aged 29 years, was admitted on August 6, 1943, in a very toxic condition, and complaining of severe rectal pain, dysuria, and the passage of blood and slime per rectum. He stated that he had received an injection for piles on July 27; 3 days later he felt very poorly, but, as he was engaged in jungle training, he tried to carry on. Eventually he reported to his doctor, who found that his temperature was 103 degrees and sent him to hospital.

On examination, apart from his rectal condition, there was found no obvious cause for his high fever and toxemia. The white blood count was 20,916 (polymorphonuclears 78 per cent, leucocytes 21 per cent). On microscopic examination of the rectal discharge, blood and pus were seen, but no sign of amebae. An anesthetic was necessary to permit examination of the rectum. Prostatic and perirectal abscesses were excluded. Very inflamed piles were seen, and the whole area within range of the proctoscope was intensely congested. Smears were examined with the same result as before.

Sulfonamide treatment failed to reduce the toxemia, and on August 13, a sigmoidoscopy was performed. On account of the intense infection, examination was restricted to the anal canal and lower part of the rectum. On this occasion smears taken from the rectal walls were found to contain the Endamoeba histolytica. Emetine was rapidly effective, and, a fortnight later, sigmoidoscopy revealed no evidence of inflammation.

This exceptional case illustrates the grave danger which may attend even such a minor surgical procedure in the presence of an amebic infection.

Fibrous stricture. Contrary to earlier opinion, the view is now held that amebic dysentery rarely produces fibrous stricture of the rectum. It is often impossible to determine the nature of the infection concerned, for, apart from conditions such as syphilis and lymphogranuloma, stricture may follow many varieties of proctitis due to nonspecific causes. Even when strictures result from amebic infections, the identification of the ameba may present great difficulty.

The only example of fibrous stricture of the rectum which occurred in our series was found in the following patient:

W. D., aged 28 years, who was admitted for proved dysentery of 4 months' duration on July 17, 1943. After treatment with emetine, carbasone, and quinoxyl he complained of increasing difficulty in passing his motions. He was found to have a double stricture, affecting the upper part of the anal canal and lower part of the rectum, which was clearly fibrous, and would only admit the little finger with difficulty. Intermittent dilatation resulted in a great improvement. Although ulceration was found between the strictures, amebae could not be detected in the scrapings from the surface or in the stools. Biopsy disclosed nonspecific chronic inflammatory changes only, and the Wassermann reaction was

negative. No certain cause was established to account for the stricture.

Amebic lesions of the rectum simulating neoplasm. In intestinal amebiasis of long-standing, multiple polypoidal excrescences of granulation tissue or edematous mucosa are sometimes seen at sigmoidoscopy, and may be mistaken for simple neoplasms. They usually disappear when emetine is used—if not, biopsy will be required for diagnosis.

In recent years attention has been focused on the chronic amebic ulcer or area of granulation tissue which may assume the clinical appearances of carcinoma of the rectum (27, 32, 43). Typical amebic ulcers are occasionally seen at a higher level, but in many cases the lesion exists alone. A short history, extensive involvement of the rectal wall, and absence of the typical induration of carcinoma, are suggestive of amebiasis, but frequent examples occur in which the clinical features cannot be distinguished from those of malignancy. Differential diagnosis includes the discovery of the ameba in the stools or in scrapings from the ulcerated surface, but the possible coexistence of carcinoma demands close observation of the effects of emetine, and, occasionally, biopsy.

This type of amebic lesion is to be expected from time to time among soldiers on their return home from endemic areas—the writer saw 6 examples during a period of 3 years in India—and on that account 2 typical cases will be described:

During the withdrawal from Burma, H. S., aged 24 years, developed abdominal pain and diarrhea. He was admitted to a hospital on arrival in India; the diarrhea had subsided, but an inflammatory mass was found in the right iliac fossa which persisted for some weeks, and appendix abscess was diagnosed. Eventually he was sent on leave, and appendicectomy was recommended when he was fit. While on leave, the pain and diarrhea returned and he was admitted to another hospital. There, the possibility of a pelvic abscess was at first considered on account of a moderate fever and the passage of blood stained mucopus which did not reveal amebae. When the surgical specialist discovered a mass in the rectum which was very suggestive of carcinoma, a second opinion was obtained.

When seen on October 15, 1942, he was still suffering from diarrhea, with an intermittent blood stained discharge. He had lost over three stones in weight, and his general condition was very low. Abdominal examination was negative, but, on rectal examination, the lower edge of an indurated mass was felt just above the internal sphincter, and, above this, an irregular ulcerated surface extended out of reach of the finger. Sigmoidoscopy disclosed an ulcer which occupied the anterior and lateral walls of the rectum between the third and fourth inches from the anus. Encroachment on the lumen rendered the passage of the instrument difficult, but the upper rectum appeared normal. Both to clinical examination and by sigmoidoscopy, the condition was indistinguishable from carcinoma. Scrapings from the ulcer showed blood and pus but no amebae, but as there was some delay before the specimens were examined, further specimens were taken on the next day, and immediate examination disclosed considerable numbers of active Endamoeba histolytica.

Treatment with emetine was rapidly effective; the diarrhea was relieved and weight and strength were regained. Repeated sigmoidoscopy confirmed the clinical improvement, and within a month the rectum had returned to normal. The patient was advised to have his appendix removed at a later date, although it appeared probable that his "appendix abscess" was in reality an ameboma of the cecum.

J. L., aged 22 years, was in hospital on two occasions in the year 1942 for amebic dysentery, and each attack responded to treatment with emetine, carbasone, and quinoxyl. He was readmitted on July 16, 1943 for a recurrence, and the Endamoeba histolytica was again found in the stools. Chiniofon and potassium bismuth iodide (Indian equivalent of emetine bismuth iodide) were prescribed, and though the stools continued loose, they were negative for amebae on February 8 and 10. Sigmoidoscopy on February 10 disclosed an ulcer with thickened edges and an irregular surface, covered with blood and slime, occupying about three-fourths of the circumference of the rectum, a short distance above the internal sphincter. The ulcer extended upward for about an inch, and to palpation and the naked eye might well have been malignant. The higher reaches of the bowel appeared normal. Scrapings from the surface of the ulcer contained Endamoeba histolytica.

Emetine was given, and 2 days later amebae reappeared in the stools. After 12 grains had been taken they were again normal. Routine treatment was completed, and at sigmoidoscopy on March 13, there was no sign of disease other than a slight tendency to bleed at the site the ulcer had occupied. On March 20 a further sigmoidoscopy presented no abnormality.

A NOTE ON SIGMOIDOSCOPY

Apart from the obvious advantage in appropriate cases of obtaining a specimen for diagnosis directly from the surface of an amebic ulcer, or for histological examination, sigmoidoscopy provides a valuable method of confirm-

ing the effects of emetine when used for diagnostic or therapeutic purposes, and for the exclusion of other lesions, such as carcinoma, which may coexist with amebiasis.

We have frequently found the Endamoeba histolytica in specimens at sigmoidoscopy when the stools had proved repeatedly negative, and have discovered still active ulceration when all other evidence indicated a complete cure from treatment. Jackman advocates routine sigmoidoscopy for every case in which amebiasis is suspected, on the grounds that the occasional coexistence of neoplasm is sufficiently frequent to warrant this step. The method is included as part of the routine investigation of amebic dysentery in British Military Hospitals in the East.

Various estimates have been given of the percentage of cases of intestinal amebiasis in which lesions may be found at sigmoidoscopy; Manson Bahr reports at least 80 per cent, while Jackman's figure is 20.8 per cent. The surgeon is more concerned with a selected group of cases in which the lesion is localized, and on that account the method is most useful in rectal and sigmoid lesions. We have had positive results in about 10 per cent of attacks which on clinical examination appear to be confined to the cecum.

For a description of the methods of preparation, the sigmoidoscopic appearances of amebiasis and their differential diagnosis, the reader is referred to publications by Manson Bahr and Biggam (4, 26, 27).

OPERATIONS IN RELATION TO INTESTINAL AMEBIASIS

Operations which involve disturbance to the bowel which has been infected by the Endamoeba histolytica are liable to be followed by certain complications related to this infection. A brief summary is presented:

Acute exacerbation of amebic dysentery. A localized amebiasis may be transformed into a diffuse type, occasionally of great severity. After intestinal suture and rectal operations the effects at the site of operation may be serious.

Local and distant septic complications. These are common and may prove fatal. Many examples appear in the literature of conditions such as pericolic abscess, gangrene of the bowel, peritonitis, and hepatic abscess, in some of which the appearances at operation gave no cause for alarm.

Intestinal hemorrhage. Barry and Crump, and Cope have emphasized the special risk of hemorrhage from amebic ulcers after operation, most commonly in cases of cecal amebiasis.

Delay or failure of the normal repair processes. Prolonged delay in healing, and spreading ulceration of the abdominal wall, were often seen before the introduction of emetine, and may occur in examples of unsuspected amebiasis. Failure at the suture line in cases of anastomosis figures prominently in the published cases. Possibly the lack of round celled and fibroblastic reaction, which is found in certain circumstances in amebic infections, is related to the incidence of these complications.

These dangers are well known, and a surgeon's individual experience is therefore limited. Three examples are described in this paper, a case of fulminating cecal amebiasis, and 2 rectal cases, but other examples have occurred among surgeons of our acquaintance. The most convincing evidence is presented in the reports of the Chicago epidemic, although it should be noted that the incidence of severe attacks was exceptionally high. In the early stages, the number of deaths following operations for suspected surgical conditions assumed such proportions that the Public Health authorities found it necessary to take exceptional measures to advise doctors, in the wide area concerned, on the diagnosis and treatment of amebiasis (5). The mortality of the 1215 cases traced was 7 per cent. McCoy reports 13 deaths among 32 patients submitted to appendicectomy, and other deaths after operation for cholecystitis and carcinoma of the colon. In all these cases amebiasis had not been diagnosed. "In 50 per cent of the fatal cases mistaken diagnoses were reported, and in more than two-thirds of these the illness had been handled as a surgical disease. In no instance did a fatality follow early consultation, prompt diagnosis, and specific treatment" (28).

In spite of these dangers, exploratory operation is occasionally necessary, as, for example, when the diagnosis between cecal and amebi-

asis and appendicitis remains in doubt. Simple exploration with no further procedure if amebiasis is found might appear ideal, but certain disadvantages must be recognized. A mildly infected cecum may show no external evidence of amebiasis, and there is a distinct possibility of treating such a case as an ordinary appendicitis. Any manipulation of the cecum may lead to a flare up of the amebic infection, but if appendicectomy is performed the risks are much increased. In severe attacks, the two diseases may present very similar appearances, and it is sometimes impossible to distinguish them at operation. Adequate exposure is necessary, and the cecum may be adherent or the appendix difficult of access—conditions which may involve manipulation and predispose to complications. In the case of a cecal ameboma, the appendix may be very adherent, the tissues friable, and bleeding may prove most troublesome—quite apart from the danger of bleeding into the cecum— and the removal of the appendix may be both difficult and dangerous.

During operation, handling of the cecum should be restricted as far as possible. If amebiasis is recognized, the appendix should not be removed unless it obviously constitutes a danger. When the appearances are inconclusive in the cecal area, typical changes may occasionally be seen in the more distal colon, but, if not, appendicectomy is generally to be advised and the contents examined at once for the Endamoeba histolytica.

The foregoing observations endorse the view previously expressed, when the indications for exploration in doubtful cases were discussed, that in endemic areas every effort should be made to arrive at a clinical diagnosis without resort to laparotomy.

In the past, indications for operations such as appendicostomy and cecostomy were described (10), for the treatment of intestinal amebiasis, which remained uncontrolled by medical measures, but, today, the majority of surgeons concur with Craig when he condemns their use. With the exception of rare complications which have not responded to the available drugs, such as anorectal fistula, colostomy is also inadvisable. These operations are all liable to the complications described here, and peritonitis is very liable to arise in the vicinity of the wound. Even when the disease is apparently confined to the distal colon, it is not possible to exclude amebiasis in the more proximal bowel

The futility of colostomy for the control of active amebic infection in the distal colon is indicated by Manson Bahr's observation: "When colostomy is undertaken in the presence of amebiasis on the mistaken impression that the symptoms are those of carcinoma, the process of amebic ulceration is accentuated rather than retarded" (27).

Appendicostomy and cecostomy have been employed for the purpose of lavage, but the advantage over the rectal route is very questionable. Neither operation provides rest to the large intestine. This object can be effectively secured by ileostomy, an operation which *may* have a limited application in selected cases resistant to other treatment (29).

To sum up: excluding perforation, abscess, and obstruction, there are few exceptions to the rule that operation is strongly contraindicated in intestinal amebiasis. These include the removal of an ameboma which fails to respond to medical treatment, the provision of a colostomy for rare cases of intractable anorectal fistula, and, possibly the performance of ileostomy in selected resistant cases of intestinal amebiasis. Interval operation may be advisable after an attack of acute cecal amebiasis, and exploration may be required in doubtful cases.

Finally, an important fact emerges from the study of the published cases—in a high proportion of those which ended fatally, emetine was omitted or only commenced late after operation, when the ameba was discovered in the stools.[1] According to Strong "the curative action of emetine often stands in direct relation to its early employment in the attack" (40). Operation may be necessary in known cases of amebiasis, and in these the sooner emetine is given the better; in reasonable doses any depressant effect on the heart is more than outweighed by the beneficial effect on the toxemia (16). When the diagnosis is in

[1] A striking feature of many of the published cases was the failure to discover the Endamoeba histolytica after operation in spite of repeated stool examinations, although postmortem examination revealed extensive acute intestinal amebiasis.

doubt, if there is strong suspicion of this disease at operation, it is unwise to delay its use until positive evidence is forthcoming.

SUMMARY AND CONCLUSIONS

Intestinal amebiasis is the disease of major surgical importance in endemic areas. With the return of the forces from the East, examples of this disease must be expected in general practice at home.

The clinical and radiological manifestations of the localized forms of intestinal amebiasis may be indistinguishable from those of surgical diseases, acute or chronic. It is usually, but not always, possible to find the Endamoeba histolytica in the stools; sigmoidoscopy may succeed when examination of the stools fails. The response to emetine is of considerable diagnostic significance, but occasionally the condition is resistant to the drug, and exploration or biopsy is then required. The possible coexistence of amebiasis with other lesions must not be overlooked.

Perforation of an amebic ulcer is to be expected in less than 3 per cent of cases. It is most often associated with fulminating infections. Toxemia may mask the clinical signs, and if gangrene is present recovery, even with operation, is very unlikely.

The clinical features of acute cecal amebiasis and acute appendicitis have much in common; the differential diagnosis may present great difficulty, but in view of the special risks of operation in cases of cecal amebiasis, every endeavor should be made to obtain a clinical diagnosis. If exploration proves necessary, manipulation of the cecum should be avoided as far as possible, and, unless the appendix is obviously in a dangerous condition, it should not be removed if amebiasis is found; emetine should be given at once after operation.

However suggestive of acute appendicitis, operation should not be advised in any case with an inflammatory mass until cecal amebiasis has been excluded. Amebic appendicitis is regarded for purpose of diagnosis and treatment as an extension of cecal amebiasis—unless complicated by abscess or perforation, it is a medical disease.

Unsuspected intestinal amebiasis and post-dysenteric conditions of nonappendicular origin often give rise to symptoms very suggestive of chronic appendicitis. Before appendicectomy is advised, these conditions must be carefully excluded. Operation is occasionally required for residual appendicular disease following cecal amebiasis.

Examples of localized chronic amebic colitis and ulceration of the rectum which may be mistaken for carcinoma or other surgical disease are common in endemic areas. Minor anorectal conditions, such as piles, fissure, and fistula, may result from unsuspected mild or chronic amebiasis.

With few exceptions abdominal or rectal operations are strongly contraindicated in patients suffering from intestinal amebiasis—they are often followed by serious complications peculiar to this disease. If operation is necessary, or if amebiasis is discovered at exploratory operation, the sooner emetine is commenced the better. Appendicostomy and cecostomy have no place in the treatment of this condition.

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THE SURGICAL TREATMENT OF INJURIES OF THE BRAIN, SPINAL CORD, AND PERIPHERAL NERVES

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Craniocerebral Injuries

THE recognition of craniocerebral injuries presents no problem. Evaluation of the extent of the damage, however, is often difficult or impossible during the first few hours after the injury. In *closed* head injuries intracranial hemorrhage is potentially present in every case. In *compound* head injuries correct appraisal is usually impossible before x-ray pictures of the skull have been taken, the clinical course observed for a period of time, or surgical exploration carried out. Small lacerations of the scalp may be associated with extensive fissure fractures, comminuted, or depressed fractures of the skull; or, with serious intracranial bleeding. This is especially true in the case of penetrating wounds which have been inflicted by small missiles.

IMMEDIATE TREATMENT

The earliest possible removal of patients with craniocerebral injuries to a hospital where intracranial bleeding can be controlled and definitive intracranial surgery as needed, can be performed, is the basic principle in the immediate treatment of these injuries. Emergency treatment has for its sole purpose the preparation of the injured man for this evacuation. Specific methods of treatment for cerebral concussion and edema are all of questionable therapeutic worth and need not be undertaken. If there are scalp wounds the hair should be cut for several inches about them with clippers or scissors, but a razor should not be used at this time. Bleeding from open wounds of the scalp can usually be controlled by firm pressure dressings. Ligature of the larger arteries of the scalp is unsatisfactory and often impossible due to retraction of these vessels into the scalp. Troublesome bleeding from this source is best controlled by mattress sutures about bleeding vessels. Wounds should not be explored, irrigated, débrided, or sutured. Sulfanilamide powder[1] should be dusted into all wounds in 5 gram quantities. Dressings of gauze should be large enough to cover the wound generously and should be firmly applied with a bandage which covers the entire head. As long as it remains in place it should not be changed until the patient reaches the hospital where definitive treatment is to be given.

Blood lost through external hemorrhage from the scalp, if great, should be replaced exactly as it is in wounds of other parts of the body. Bleeding from the ears should be treated simply by covering the external ear with a large loose gauze dressing. No effort should be made to stop this bleeding. The auditory canal should not be explored, mechanically cleaned, or irrigated. Neither cotton nor gauze should be introduced into the canal.

Shock is rarely the result of craniocerebral injury. Its presence usually indicates bleeding or trauma in other parts of the body. In these cases the head should not be placed lower than the trunk and the extremities since this position will aggravate intracranial bleeding. Otherwise, shock associated with craniocerebral injuries should be treated without regard to the brain injury. Blood and plasma should be given as needed until the blood pressure levels approximate normal.

The unconscious patient should not be transported lying upon his back. In this position he may aspirate mucus and vomitus into his lungs and may have his airway obstructed by the tongue. He should be horizontal, lying on his side, his body rotated well forward, his upper thigh flexed on the pelvis to hold him, his head resting on a firm pillow or folded blanket and turned toward the ground. This position will prevent the tongue

[1]There are reports in the literature that sulfathiazole and sulfadiazine applied directly to the brain may produce convulsions, but in practice a large experience by the British in the Middle East campaigns has not confirmed these observations.

from falling back and interfering with respiratory exchange. It will also prevent aspiration of mucus and vomitus and will greatly reduce the hazard of aspiration pneumonia. In compound wounds the patient, as a rule, should lie only upon the uninjured side of the head. Conscious patients may have the head and shoulders elevated.

Morphine and other opium derivatives are contraindicated in cases of severe craniocerebral injury because of their strong depressant action on the respiratory center of the brain. The soporifics, such as chloral hydrate, paraldehyde, and amytal are contraindicated because their use masks the significant changes in the patient's state of consciousness which are of prime importance in determining the presence of intracranial bleeding and the indications for operation. Fortunately, pain is rarely a serious problem in craniocerebral injuries, closed or open, unless they are complicated by serious injuries to other parts of the body. When wounds of the thorax, abdomen, or extremities do cause great pain the first considerations should always be to relieve the pain but to use the smallest amount of morphine which will effectively accomplish this.

Restlessness presents serious problems in the care of craniocerebral injuries especially during transportation; and if violent may result in serious harm to the patient. Sodium luminal, 3 to 5 grains (0.2 to 0.3 gm.) given hypodermically is the best drug to allay restlessness in that it will quiet the patient without depressing the respiratory center or greatly disturbing his state of consciousness. Sodium bromide, or the triple bromides, 15 to 30 grains (1 to 2 gm.) by mouth or 45 to 60 grains (3 to 4 gm.) per rectum are also of value. If neither of these drugs is available, morphine may be given in small doses 1/8 to 1/6 grain (0.008 to 0.010 gm.) and repeated after 30 minutes if necessary, provided the respiratory rate remains above 16 per minute.

One thousand to 1500 cubic centimeters of fluid each 24 hours should be given to all patients and if the patient is unconscious or is vomiting, this should be given either by means of the rectal drip or by slow intravenous administration.

The first doctor to treat the patient with a serious craniocerebral injury should record the following facts without fail: (1) time of injury as nearly as can be determined; (2) state of consciousness—is the patient rational, restless, confused, drowsy, stuporous or comatose; (3) paralysis—does the patient move both arms and both legs voluntarily or in response to painful stimuli; (4) aphasia—does the patient talk or is he conscious but unable to talk; (5) pulse rate counted for half a minute; (6) respiratory rate counted for a full minute; (7) blood pressure.

Transportation to a hospital where definitive neurosurgical care can be given the patient should be initiated as early as possible. With sulfonamide therapy a primary closure of craniocerebral wounds can be carried out safely as late as 48 to 72 hours after injury. Air transport below 3,000 feet altitude is perfectly safe. These patients tolerate transportation very well, particularly before a definitive operation has been performed. It is more important that definitive care be given by a well qualified and experienced neurological surgeon under favorable conditions than that it be given early.

Under conditions of warfare, it is usually best, even though this procedure requires 24 to 48 hours of travel, to evacuate craniocerebral injuries directly to an evacuation or general hospital located at a safe distance from the combat area where there are highly trained surgical and nursing personnel, where x-ray and operating room facilities are superior, and where patients can be held 7 to 10 days after operation before they are again moved.

DEFINITIVE TREATMENT

The term "concussion of the brain" is here used in a broad sense to designate the entire "complex" of ill defined and incompletely understood pathological processes, other than gross hemorrhage, which contribute to, or are associated with disturbances of consciousness following cranial trauma, including so called "axonal disruption," edema of the brain, and cerebrospinal fluid hydrops. The pathological and clinical manifestations of concussion appear immediately after injury and almost always become maximum within the first few

hours. Patients who make a satisfactory adjustment during this initial period usually survive.

Generally accepted and well authenticated specific treatment for cerebral concussion does not exist. Surgical decompression is ineffective and often harmful and should not be performed. Lumbar puncture for therapeutic purposes is of questionable value but the cautious removal of 1 to 2 cubic centimeters of spinal fluid for diagnostic purposes is permissible. Intravenous hypertonic glucose or sucrose solution (100 cubic centimeters of 50 per cent glucose or 200 cubic centimeters of 50 per cent sucrose) has only a temporary effect and some undesirable side effects. Frequently repeated administration is contraindicated because of possible renal damage. Magnesium sulfate (25 per cent solution, 150 to 200 cubic centimeters) given by rectum is an effective means of combating concussion in many instances but it is an expensive procedure both in linen and labor and its general use is not encouraged.

Supportive treatment is very important. If this is adequate, the great majority of patients suffering from posttraumatic cerebral concussion, uncomplicated by gross hemorrhage, will survive. Fluids must be given to meet the basic metabolic requirements in all patients with craniocerebral injuries. One thousand cubic centimeters per day may be regarded as the absolute minimum and 1500 cubic centimeters per day as the desirable average. During hot weather or periods of hyperpyrexia the amounts should be increased to 2500 to 3000 cubic centimeters. Fluids should never be put into the mouth of unconscious or stuporous patients but should be introduced by rectal instillations, hypodermoclysis, or very slowly into a vein. Not more than 1000 cubic centimeters of the fluids given intravenously during a single 24 hour period should be in the form of physiological saline solution. When intravenous fluids are given in excess of this amount they should consist of 5 per cent glucose in distilled water.

Nutrition must be sustained. During the first 48 to 72 hours after the injury, however, the patient will need to be given only fluids (1500 to 2500 cubic centimeters) and glucose (80 to 100 grams). After 72 hours the patient will need, in addition to fluids and glucose, 60 to 80 grams of protein daily and sufficient fats to make up his caloric requirements. The fat requirement may be obtained, temporarily, in whole or in part from the fats of the patient's own body; but the proteins must be supplied to the patient, most conveniently in the form of egg albumin given by the stomach tube. In the unconscious or the stuporous patient feedings must be given by the stomach tube because attempts to feed this type of patient by placing food in the mouth are frequently followed by aspiration and pneumonia.

The prevention of aspiration pneumonia in the unconscious patient depends largely upon his position in bed. He should be placed on a firm, flat bed, preferably a "fracture" bed, and supplied with a hard pillow. He should never lie on his back, but rather on his side with the upper leg flexed, the body rotated well forward, the face down, and the jaw and tongue dependent. In this position all mucus from the uppermost lung and bronchus, the trachea, the pharynx, and the mouth will drain freely out and the tongue will not interfere with the airway. Unconscious patients should be turned from one side to the other every 4 hours at least, and preferably oftener, day and night.

The prevention of pressure sores of the skin and subcutaneous tissue will also be greatly aided by turning the patient frequently. In each position, bony prominences must be protected from direct pressure of the bed or from other extremities. Tissues which have borne the weight of the body should be gently massaged with a well greased hand after each turning to restore the circulation more fully. The patient should be placed on an air mattress whenever one is available.

Intracranial hemorrhage. Intracranial hemorrhage as a complication of closed craniocerebral injuries should be suspected in every patient who continues to get progressively worse following a blow to the head. It may be epidural, subdural, intracortical, or intracisternal in location.

Epidural hemorrhage should be suspected with fractures of the vault. The bleeding is

arterial, from torn branches of the middle meningeal artery, and hence is apt to be rapid. This requires early recognition and treatment. A negative exploration is better than one too late. Neurological signs may be generalized, contralateral, or ipsolateral. Hence, bilateral exploration is usually indicated. The site of election for exploratory trephination is just above the middle of the zygoma, exposing the main trunk of the middle meningeal artery. If the artery is torn close to the foramen spinosum, it may be necessary to plug that foramen with bone wax and the surgeon should be prepared to do this. Considerable blood may be lost before the bleeding point is controlled; hence, a donor should be present if possible. Small exploratory incisions may be made in the dura mater but it should not be opened widely at this time because rupture of the edematous cortex may result. Drainage down to the dura mater for a period of 24 hours may be useful.

Subdural hemorrhage is usually venous and occurs from torn cortical or subcortical veins. It rarely is under sufficient pressure to cause death and it usually stops spontaneously. Hence, early evacuation is not so necessary as it is with epidural (arterial) bleeding; it may often be delayed profitably until cerebral edema has subsided. Since the site of bleeding in young adults is usually the anterior pole of the temporal lobe, exploration of the floor of the middle fossa is indicated and this is best exposed through a small osteoplastic flap after the period of acute edema of the brain has subsided; that is, 5 to 10 days after injury.

A chronic subdural hematoma should be suspected in every patient with a head injury when satisfactory initial progress becomes arrested, or whose condition actually deteriorates. These clinical changes may manifest themselves 1 to 6 weeks after the injury, occasionally later. The symptoms and signs are usually vague and often fluctuate from day to day or hour to hour. Under such circumstances, bilateral exploratory trephination should be performed and the liquefied clot evacuated. Occasionally an osteoplastic flap is necessary if the clot has organized.

Intracortical hemorrhage, if arterial, is apt to dissect into the ventricles and be rapidly fatal. If venous, it tends to form large subcortical clots and then to stop spontaneously. These occur in the temporal lobes in 90 per cent of the cases, equally on the right and left sides, and almost as often *contre-coup* as on the side of the blow. These venous clots are rarely fatal. They are characterized clinically by preponderance of the focal signs over those of general intracranial pressure, the exact reverse of the clinical picture produced by surface clots. They are frequently associated with a subdural clot of moderate size. The presence of subcortical clots may be determined by pneumoventriculography; or, at operation, by means of exploratory puncture, or incision into the temporal lobe. Prognosis for the recovery of function after evacuation is favorable even after many weeks have elapsed.

Intracisternal hemorrhage is frequently associated with fractures at the base of the skull. Bleeding is usually from a tear in one of the large communicating veins leading from the cortex into a dural sinus and takes place directly into one of the subarachnoidal cisternae. Since this is venous bleeding it is not under great pressure. However, fatal results from this type of bleeding are frequent, and are due to the fact that the large number of red blood corpuscles in the spinal fluid tend to block the channels over the cerebral hemispheres from which the cerebrospinal fluid is absorbed. The result is an acute hydrocephalus similar in character to the so called communicating type seen after meningitis in which postinflammatory adhesions of the subarachnoid spaces similarly interfere with the normal absorption of spinal fluid. Pressure signs usually do not appear critical until 12 to 24 hours after injury. Bleeding from the sinuses may be lessened by elevating the patient's head and shoulders. Spinal puncture is ineffectual in recovering the offending blood corpuscles at the point of actual obstruction over the surface of the cerebral hemisphere, and possibly encourages fresh bleeding by temporarily lowering the pressure applied against the bleeding point. There is no accepted surgical measure to be taken against this type of intracranial bleeding, and the prognosis has been

considered largely inherent in the injury itself. It may be that temporary drainage of one or both lateral ventricles by means of small catheters introduced through trephine openings may prove of value. General supportive measures similar to those outlined under the treatment for cerebral concussion are indicated.

Physical and mental rehabilitation of patients who have received a craniocerebral injury requires good judgment and skill. The patient must be encouraged in every way to think that the injury has been only a slight one. Terms like "concussion of the brain" and "compound fractures of the skull" must be absolutely forbidden, and in the presence of the patient such simple terms as "bump on the head" and "cut on the head" substituted. Lumbar punctures in conscious patients are usually unnecessary and are particularly to be avoided. They add little useful knowledge, have little therapeutic value, and leave a deep and bad psychological scar. An arbitary period of bed rest for 2 to 3 weeks, as was formerly practiced, is no longer approved. Instead, as soon as the patient feels able to sit up or go to the lavatory, or to have his meals, he should be allowed to do so. He should be encouraged to participate in the care of his room and his own person. Physical therapy including passive motion, baking, massage and electrical stimulation, should be directed to paralyzed limbs.

Wounds of the scalp. Every wound of the scalp, no matter how small, may be a penetrating wound of the skull with injury to the brain. Therefore, x-ray pictures of the skull should be taken in every case of craniocerebral injury before definitive treatment is begun to establish the presence or absence of concealed fractures, indriven fragments of bone, or retained missiles.

Primary closure of wounds should be attempted in every possible case. Each wound of the scalp may be needed later as a portal of entry into the intracranial cavity in search of intracranial bleeding. Primary closure may be properly attempted as late as 48 hours following the injury in wounds which have not received any emergency treatment with the sulfonamides, provided careful débridement is carried out and vigorous systemic sulfonamide therapy is instituted after the operation. Wounds which have received preliminary treatment with the sulfonamides may be closed as late as 72 hours or even 96 hours after the injury. Standard neurosurgical procedures should be followed with conservative débridement and meticulous approximation of the skin edges. Sulfanilamide powder may be lightly dusted into the wounds before closure. There is, however, a general and growing conviction that, with adequate systemic chemotherapy, the local administration of sulfanilamide powder is unnecessary and even undesirable.

Drainage should be employed rarely with wounds of the scalp and only for the purpose of relieving tension by evacuating fresh blood. Drains do not prevent infection, they frequently introduce it. When drains are used in noninfected wounds of the scalp they should be led out through stab wounds and should be removed not later than 24 hours after the operation.

Fractures of the skull. Simple linear fractures of the skull are of little consequence in themselves, apart from the concomitant injury to the intracranial contents. They are, however, frequently associated with intracranial hemorrhage; those of the vault with epidural bleeding from a torn meningeal artery, and those at the base, with bleeding into the basilar cisternae from large veins or venous sinuses.

Compound linear fractures are important because they afford a portal of entry for infections into the intracranial cavity. This is especially true of fractures compounded through the cribiform plate, the accessory air sinuses, or through the external auditory canal. Hence, it is important to institute early and vigorous chemotherapy in all such cases. Bleeding from the ear indicates a compound fracture into the external auditory canal. Gross clots plugging the peripheral portion of the canal may be removed gently, but no attempt should be made to explore the canal. clean it, or even irrigate it. No cotton or gauze should be placed in the canal. The external ear should be covered with a flat sterile gauze dressing.

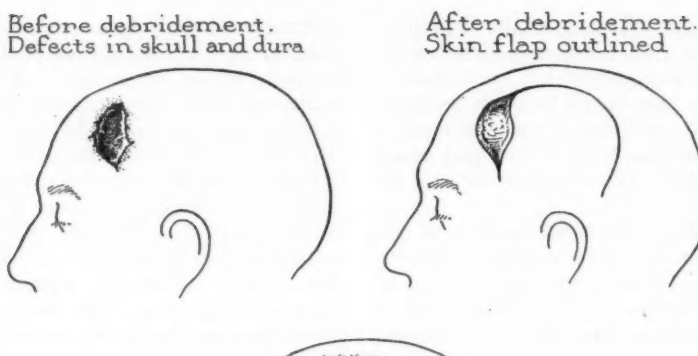

Fig. 1. Method of closing defect in scalp by "sliding flap" method.

Simple comminuted (depressed) fractures should be elevated early to avoid the effects of both general and local pressure upon the brain. Compound comminuted (depressed) fractures are frequently accompanied by perforation of the dura mater and laceration of the brain. X-ray studies are mandatory before definitive care is instituted. In treating these cases scalp, skull and dura should be débrided carefully, foreign matter should be picked out, devitalized brain removed with the sucker, hemorrhage arrested, the dura mater repaired, and the scalp closed. Drains should, as a rule, not be necessary but if used, they should be brought out through separate stab wounds and removed altogether during the first 24 hours. In cases in which sulfonamides have not been administered at all prior to operation, primary closure may be attempted at any time during the first 36 hours after the injury provided that maximum systemic sulfonamide therapy be carried out postoperatively. In those cases in which sulfanilamide powder has been introduced into the wound as part of emergency treatment soon after the injury, primary closure may properly be undertaken as late as 72 hours after the receipt of the injury in the majority of instances.

Closure of the dura mater and scalp is to be sought in all cases. Large dural defects should be closed by "split-dural" flaps, or with free transplants from the temporal fascia, the pericranium or the fascia lata. Penicillin (10,000 units), if available should be introduced inside the dura upon the underlying and adjacent brain.

The closure of wounds of the scalp can be accomplished in most instances after extensive mobilization of the scalp between the galea and pericranium. If, however, this does not suffice then the best way to close a defect in the scalp usually is by means of a "sliding flap" of scalp having the shape of an elongated horseshoe (Fig. 1). The flap should not include the pericranium. In outlining and cutting such a flap it is important to make it considerably oversized in both transverse and longitudinal directions, because of the complete inelasticity of the tissue. If great care is not exercised in doing this the edges intended to be apposed will not meet. The base of the flap should be wide to insure adequate blood supply to its periphery. Edges of the flap not

sutured to the scalp should be loosely sutured to the pericranium. Drains usually need not, and should not, be used. The pericranial surface left exposed after moving the flap should be covered immediately by a Thiersch graft, or a skin graft of intermediate thickness. Such grafts are successful in a very high percentage of cases. In the rare cases in which they do not succeed, the exposed bone will be covered quickly with granulations if numerous small drill holes are made through the outer table to the diploic spaces. These granulations can subsequently be covered with pinch grafts or other types of skin grafts. Sulfanilamide powder should not be used locally, but vigorous systemic sulfonamide therapy instituted.

Compound comminuted fractures into the accessory nasal sinuses present troublesome problems. No rule can be laid down for treatment which will meet the specific needs of every case. In general, however, the principle should be to repair the scalp and dura mater exactly as in compound, comminuted fractures in other parts of the cranial vault and to do as little as possible to the sinus. In dealing with the sinus it is almost axiomatic that "the less the surgery, the less the trouble." The contour of the sinus should be re-established as far as possible by gentle manipulation with the smooth rounded end of a hemostat or any other similar instrument. Comminuted portions of the bony walls should be preserved wherever possible and only fragments of bone entirely detached from all soft tissues should be discarded. The mucous membrane lining the sinus should be carefully conserved, even though badly torn, because of the great power of regeneration possessed by this membrane and its strong tendency to re-form a functioning air sinus. The frontonasal ducts should not, as a rule, be touched. Drains should not be used. The danger of serious intracranial infection is generally less than might reasonably be expected if sulfonamide therapy be aggressively employed. The administration of sulfanilamide powder locally in small amounts is recommended in these cases, in addition to the systemic administration of the sulfonamides.

Repair of defects of the frontal bone resulting from compound comminuted fractures in this region either with tantalum or by bone grafts should not be attempted at the time the acute injury is treated.

Rhinorrhea of cerebrospinal fluid persisting for longer than 5 days should be treated by intracranial closure of the internal orifice of the fistula by fascia transplant as soon as a craniotomy may safely be performed. Sulfadiazine should be administered systemically. Maximum chemotherapy should be instituted early and maintained for 10 to 14 days after operation.

Penetrating wounds of the brain. The basic principles outlined for the treatment of wounds of the scalp, compound fractures of the skull, cerebral edema, and intracranial hemorrhage apply equally to the treatment of penetrating wounds of the brain. Hemorrhage and shock should be treated according to established principles. Roentgenograms of the skull should be studied before definitive treatment is undertaken.

Penetrating wounds, when received for definitive treatment, may be either "fresh" or "old." The fresh cases include those not having received preliminary local or systemic treatment with sulfonamides but which present themselves for definitive treatment not later than 36 hours after the wound was received and without signs of active sepsis in the wound at that time; also cases which have received adequate emergency sulfonamide therapy at the time of injury, or soon after, presenting for definitive treatment not later than 72 hours after the injury was received, without signs of active sepsis in the wound at that time.

Early penetrating wounds of the brain should have definitive surgery at the earliest possible moment. The entire head should be shaved immediately before operation. A large area of scalp should be cleansed and so draped that any plastic procedure which might be necessary to close the wound, such as a large sliding skin flap, may be performed. Débridement of the skin should be conservative. All loose fragments of bone should be discarded. The openings in the skull and dura mater should be enlarged. Devitalized cortex should be excised. The tracts of all large missiles within the brain then should be thoroughly

explored. Dirt, hair, particles of clothing, fragments of bone, old blood clots, and devitalized brain must be cleaned out, after which the tract should be thoroughly irrigated with physiological saline solution. Damaged and contaminated brain lining these tracts may be removed with a blunt curette or a sucker. Penicillin (10,000 units) should then be introduced into the full length of the tract. The opening in the dura mater should be closed tightly by the use, if necessary, of free grafts of the patient's temporal fascia, pericranium or fascia lata, held in place with fine silk sutures. Primary suture of the skin must be accomplished over defects in bone and dura mater. If there has been loss of tissue of the scalp some standard form of plastic repair of the defect must be employed, such as a sliding skin flap.

Penetrating wounds of the brain involving the frontal and ethmoid sinuses, the anterior nares, and the orbital fossae demand special consideration. Principles governing the care of compound comminuted fractures of this region, already discussed, naturally apply to these wounds. However, in penetrating wounds, closure of the opening through the dura acquires maximum importance, and is really the crux of the successful treatment of these cases. In order to close this dural defect, it will usually be necessary to provide an opening through the frontal bone on the affected side, large enough to expose the anterior pole of the frontal lobe and the floor of the frontal fossa. If the original opening in the skull made by the missile be high in the frontal region extending well above the supraorbital ridge, this original opening may simply be enlarged with rongeurs. If, on the other hand, the tract of the missile has involved only the bony structures of the floor of the anterior fossa, and not the anterior wall, then surgical exposure of the fossa should be through a small osteoplastic flap. The dura, when exposed, should be opened sufficiently to admit exploration of the anterior pole of the frontal lobe and the floor of the frontal fossa, including the portal of entry of the missile. Bone, dura, and brain about this opening should be débrided; and a careful "toilette" of the free space between brain and dura made. Unfortunately, the direction of the tract of the missile is usually such that its exploration is impossible without making fresh, deep incisions through the brain, a measure which is rarely justifiable. A free graft of temporal fascia, pericranium, or fascia lata should be laid over the defect in the bone made by the missile. This graft should be large enough to allow generous overlap at all margins. Only rarely will it be possible to suture the graft in place effectively. However, this is not necessary, for if the graft be large enough, and not too much brain tissue has been lost as a result of the injury or by débridement, the weight of the released frontal lobe, and its slight tendency to expand after the retraction, will hold the graft securely in place until fibrinous union between it, dura, and exposed bone takes place. The surgical incision made through the dura should then be closed with fine silk sutures. Penicillin (10,000 units in 2–3 c.c.) should be introduced into the subdural space. The local use of sulfanilamide in the region of the graft is undesirable, since it will attract fluids which may loosen the graft. The galea and the scalp should be closed with interrupted fine silk sutures, without drainage. Maximum doses of sulfadiazine and penicillin should be given systemically for 10 to 14 days after the operation. Great care should be taken to prevent upper respiratory tract complications during the postoperative course since violent sneezing or coughing might dislodge the graft.

The removal of bony fragments from the brain is of the utmost importance. Experience has shown that cerebral abscesses develop around 50 per cent of bone fragments not removed. The smaller metallic fragments constitute no such danger and attempts to remove them should not be made at the risk of damaging healthy cerebral tissue. It is desirable, however, to remove the larger missiles when this is surgically feasible.

Cerebral abscess should be suspected whenever normal recovery from a penetrating wound of the head is arrested. Pneumoventriculography may properly be performed under such circumstances. If an abscess be present it should be treated by any one of the standard methods.

Late penetrating wounds of the brain are those not included in the above categories. The majority will be septic. In addition to cellulitis of the scalp many will already have developed osteomyelitis, cerebritis, meningitis, cerebral abscess, or cerebral herniations and fungi. Treatment of these conditions will of necessity be determined by specific indications in the individual cases; hence, procedures will vary with each patient and for each complication. Cellulitis of the scalp should be treated with chemotherapy and in accordance with standard surgical principles. Osteomyelitis of the skull requires free dependent drainage of the bone and the adjacent covering soft tissues, with removal of sequestra as they form, in addition to intensive chemotherapy. Radical "bloc" resection of large portions of the skull usually gives disappointing results and is not advocated. Preliminary studies with penicillin indicate that it may be particularly effective in the treatment of osteomyelitis. Sulfonamide therapy should be used actively. Meningitis and cerebritis can be treated only by the sulfonamides and penicillin but respond favorably in a majority of cases. Cerebral abscesses may be treated by whichever one of the commonly accepted methods the neurological surgeon prefers. Abscesses secondary to penetrating wounds are usually due to retained bone fragments or other foreign matter along the tract of the missile. Exploration of the tract with removal of bone fragments and foreign material, followed by a short period of drainage, is the method of choice and offers a good prognosis for rapid healing.

Pathology and treatment of cerebral herniation.—Cerebral herniation and fungus formation occur whenever there is a defect in the dura mater, bone, and skin overlying the brain and is due to the fact that no structure opposes the intracranial pressure which tends to push the brain out through the defect. Cerebral herniations invariably become infected and there is usually some necrosis of superficial tissue due to interference with the blood supply entering the herniation. A cerebral herniation which thus becomes infected and partially necrotic, is designated as a cerebral fungus. If the intracranial pressure remains normal, the outward extrusion of the herniation or fungus as a rule gradually comes to rest, the necrotic tissue is removed by natural processes, and the surface of the brain becomes covered with granulation tissue and eventually scar tissue. This scar tissue in time contracts with sufficient force to counteract the expanding action of the intracranial pressure and will, in favorable cases, finally reduce the hernia completely to the general contour of the cranium. It then remains only for the surface of the scar tissue to become epithelialized, which may take place spontaneously from the edges of normal skin, or may have to be accomplished by grafting.

The primary object in the treatment of cerebral herniation is to keep to a minimum the protrusion of cortical tissue through the defect in the skull. In attempting to achieve this end, effort should be directed primarily at minimizing expanding pressure within the skull, rather than by attempting to hold the brain within the cranial cavity by applying pressure against it from without by means of pressure dressings. This latter procedure is almost always ineffective against continuous and elevated intracranial pressure and in addition, causes pressure necrosis of the herniating brain and greatly increases the amount of local sepsis in the brain tissue.

Measures for reducing intracranial tension should include maintaining the patient in a sitting posture in bed whenever possible. Spinal drainage with removal of 30 to 50 cubic centimeters of spinal fluid should be performed twice daily for 2 to 4 weeks until necrotic and infected tissue has been removed from the surface of the herniation and the exposed brain is covered with a clean layer of granulation tissue. Great care must be exercised to keep the patient from acquiring upper respiratory infections which will force him to cough and thus violently force protrusion of a cerebral hernia. Also, similar precautions must be taken against nausea and vomiting. The bowels must be kept open with the aid of laxatives, since straining at stool and even the administration of enemas, greatly increases intracranial pressure.

Local sepsis must be aggressively combated. Wet compresses, Dakin's solution or sulfona-

mide dressings should be applied to the surface of the herniation or fungus until all necrotic tissue has been removed and exposed brain has been covered by healthy granulation tissue. Thereafter the granulating surface should be treated as any other granulating surface, the essential principle being the use of a lubricated dressing which will not interfere with the ingrowth of epithelium over the margins of the wound. Superficial marginal abscesses must be constantly looked for and effectively drained when present. These are apt to occur beneath the overhanging edges of scalp, bone, or dura mater. In the very beginning it is important to have the opening in the bone larger than the opening in the dura mater and the opening in the scalp larger than the opening in the bone in order to prevent abscess pocketing by overhanging tissue.

The herniation must be protected from direct pressure by a firm ring of cotton or gauze. Direct pressure will produce necrosis and an increase of local infection. As superficial tissue is lost through necrosis and sepsis, the lateral wall of the ventricle is approached and the danger of meningitis and rupture of the ventricle with leakage of spinal fluid becomes imminent.

Persistently progressive herniation after 3 to 4 weeks of proper treatment, or excessively rapid herniation, indicates pathologically elevated intracranial pressure. This is usually due to the presence of an intracranial abscess which may be extradural, subdural, or intracerebral. X-ray evidence of retained bone fragments may reveal the site of the abscess. If the plain x-ray films offer no help, pneumoventriculography is indicated.

A new, alternate method for the treatment of cerebral herniation has recently been advocated. This consists of forcibly reducing the herniation and holding it in place within the cranial cavity by means of a perforated tantalum plate which is securely fixed into the defect of the skull. The irritating effects produced by gauze or other types of restraining dressings is greatly minimized with such a "tantalum dressing"; and the vicious pathological cycle resulting from progressive or continuous herniation is avoided. The outer surface of the tantalum plate is, in turn, covered by a sliding flap of scalp. The complications from infection which might reasonably be expected, are reported to be infrequent. Despite obvious objections, this procedure has much in principle to recommend it. It is too soon, however, to make a final appraisal of the method at this time, although reports to date make further application in selected cases justifiable.

Spinal Injuries

IMMEDIATE TREATMENT

Injuries of the cervical spine resulting from indirect trauma are almost invariably forward dislocations of the head and upper part of the cervical spine upon the lower part with a pathological anterior angulation at the level of the lesion. In the production of this injury one or more of the articulating facets of the involved vertebrae may be chipped off, but these small fractures must always be regarded as secondary to the dislocations. Determination of the exact level of the fracture-dislocation is unimportant for the emergency treatment.

The diagnosis of fracture-dislocation of the cervical spine should always be suspected whenever an injured man complains of severe pain in his neck. The diagnosis should be made definitely whenever an injured man is unable voluntarily to move either his arms or legs.

The most important principle in the emergency treatment of fracture-dislocations of the spine is to do nothing which will increase the bony deformity. Do not move the patient unless absolutely necessary for each new movement may cause bone to cut into the spinal cord. Do not raise the patient's head to give him a drink or a cigarette. Do not put a rolled blanket or pillow beneath the head. Do not lift the patient off the ground unless he is on a litter or other rigid support. Reduction should not be attempted. Plaster casts should not be applied.

The patient with a fracture-dislocation of the cervical spine is in the optimum position when he is lying on his back, with a folded blanket 3 to 4 inches thick beneath his shoulders, with his head below the level of his shoulders and his neck in slight dorsiflexion

(hyperextension). Folded blankets should be secured at both sides of the head to prevent lateral movement. A patient with a fracture-dislocation of the cervical spine should not lie face down with his neck twisted, nor upon his side with his neck flexed laterally. Care should be taken that clothing and blankets are smooth beneath the patient. Pockets should be emptied.

Three persons are needed to turn properly a patient with a fracture-dislocation of the neck onto his back from some less favorable position. The senior of the three men should grasp the chin and occiput and exert steady traction in the line of the long axis of the body. The second man should grasp the ankles and exert equal countertraction along the axis. The third man should then kneel beside the patient, reach across his body and grasp the patient's clothing near the shoulder and near the hip joint with his two hands. He should then gently rotate the patient toward himself while the men at the head and feet exert their traction. The head, neck, body, and legs should all be made to move simultaneously. A folded blanket 3 to 4 inches thick should be so placed on the ground or the litter that the patient's shoulders finally come to rest on top of it when rotation has been completed. This position will allow the head to hang down slightly and permit a moderate dorsiflexion (hyperextension) of the cervical spine —a position which tends to correct the deformity caused by the fracture-dislocation.

A patient with a fracture-dislocation of the cervical spine should never be lifted from the ground on to the litter; he should be rotated or pulled on to it. In transferring a patient from the ground to the litter, the latter should be placed beside the patient. If he be lying face down upon the ground, he may be rotated on to the litter in the manner described in the preceding paragraph, coming to rest on his back with the folded blanket beneath his shoulders. If the patient be lying face upward on the ground, the three men should take the same positions as for turning him, with the exception that the man at the side should grasp the patient's clothing on the side nearest to himself. The three men then gently slide the patient from the ground on to the litter without lifting him, the two men at the head and feet meanwhile maintaining a strong longitudinal traction.

The prevention of pressure sores is a major problem in all paralyzed patients. Efforts should be made from the beginning to keep pressure off the sacrum and the heels. Whenever possible, the paralyzed patient should be placed upon an air, or other soft mattress during transportation.

Urinary retention is common with spinal cord injuries. Extreme distention of the bladder must be avoided. An inlying catheter should therefore be introduced before distention of the bladder occurs and especially before transportation of the patient to a distant point is initiated. The catheter must never be clamped. If cystitis should develop it will not become serious as long as drainage is free; and it can be readily cleared up with the aid of tidal drainage and sulfonamide therapy at the hospital to which the patient is taken. Cystotomy should not be performed.

Morphine should not be given to patients who have received injuries to the cervical spinal column.

All patients with fracture-dislocation of the cervical spine should be transferred as early as possible to a hospital where definitive neurosurgical treatment can be given.

The common lesion of the lumbar spinal column is a compression fracture of the body of the first lumbar or adjacent vertebrae. This results in an anterior angulation of the spinal column which causes compression of the spinal cord. Dislocation between the vertebrae is uncommon at this level. The diagnosis should be suspected whenever an injured man complains of a severe pain in his lumbar spine and should be made definitely whenever such a man is unable voluntarily to move his legs.

The fundamental principles for the emergency treatment of compression fractures of the lumbar spine are essentially the same as for fractures of the cervical spine. The patient should not be moved unless it is absolutely necessary. He should not be picked up and carried from one place to another unless he has first been placed upon a litter or other rigid structure. There are two acceptable positions for a patient with a compression

fracture of the body of one of the lumbar vertebrae. If an air mattress is available, the patient should be placed upon it, lying upon his back, with 2 or 3 folded blankets underneath the air mattress at the site of the fracture so placed as to produce hyperextension of the spine. If an air mattress is not available then the best position for transport is the face-down position. This position automatically prevents further anterior flexion of the lumbar spine. It also prevents the formation of pressure sores at the point of angulation of the spine and over the sacrum. However, in this position the toes, knees, and genitals must be protected against pressure. No other attempt at correction of the bony deformity should be made at this time. Plaster casts should not be applied to any patient with a spinal cord injury having anesthetic skin.

The principles involved in turning a patient with a compression fracture of the lumbar spine are similar to those for turning a patient with a fractured cervical spine, except that in fractures of the lumbar spine, traction by the man at the head of the patient may be applied under the armpits. In transferring the patient from the ground to the stretcher the same principles apply as in the case of a patient who has a fracture-dislocation of the neck.

The principles which underlie the prevention of pressure sores, and the care of the bladder in patients with a compression fracture of the lumbar spine are the same as those which apply to the patient with a fracture-dislocation of the cervical spine. Morphine may be given as necessary to control pain and the patient should be transported as early as possible to a hospital where definitive neurosurgical treatment can be given.

Compound injuries of the spinal column are usually the result of gunshot wounds. No attempt at definitive treatment should be made at the site of the accident. Sulfanilamide powder should be dusted lightly into the wound. Large protective dressings should be securely applied. In all other respects the patient should be treated and transported in accordance with the principles outlined for the care of closed spinal injuries. Since penetrating wounds of the spine are frequently associated with wounds of the lungs or abdominal viscera, such complications should be looked for and treated appropriately.

DEFINITIVE TREATMENT

Quantitative relationship between injury to bone and injury to spinal cord does not exist. The differential diagnosis between anatomical severance of the cord and a simple and temporary physiological interruption of function is often difficult or impossible to make clinically during the early posttraumatic period. Hence, the dictum that all cases of paralysis following spinal injury must be treated as though they were suffering from a recoverable lesion until proved otherwise.

The neurological signs present after spinal injury may be due to any one, or a combination, of the following pathological factors: (a) edema of the cord, (b) hemorrhage into the cord, (c) compression of the cord by displaced vertebrae, and (d) anatomical section of the spinal cord.

Edema of the spinal cord occurs with every serious injury of the spine. It develops rapidly and is often extreme. Within an hour after injury the spinal cord may be two or three times the normal diameter so that it fills the dural envelope tightly. This is the most common cause of manometric block (positive Queckenstedt sign) during the first few days after injury. If the dura mater is opened at this time spontaneous rupture of the spinal cord with anatomical loss of continuity may result. A manometric block, therefore, should not be considered as an indication for laminectomy during the acute posttraumatic period. The clinical signs produced by severe edema of the cord are indistinguishable from those produced by transection of the cord during the first 24 to 48 hours after injury. They tend to improve after the 4th or 5th day and complete functional recovery from total paralysis may follow quickly.

Hemorrhage may occur into the extradural, subdural, and subarachnoid spaces but in these sites it rarely causes compression of the cord or produces neurological signs of clinical significance. Hemorrhage into the cord itself is limited almost invariably to the central grey matter (hematomyelia). Here bleeding

may dissect its way up and down the grey matter for a number of segments. The clot thus formed never attains sufficient diameter to cause compression of the long tracts adjacent to it, or to require decompressive measures. It produces its effects by disrupting neurones and reflex arcs at segmental levels, producing motor effects of the lower motor neuron type, i.e., flaccid paralysis, muscle atrophy, and hypotonic reflexes. After liquefaction and absorption of this clot some return of function may be expected in the affected reflex arcs. Surgical evacuation of these intraspinal blood clots produces irretrievable damage to segmental neurons and reflex arcs, and this procedure, therefore, should not be performed.

Compression of the cord by displaced bone is a less frequent cause of persistent paralysis following spinal injury than is generally assumed to be true. This is because the bony neural canal is so much larger than the spinal cord that considerable encroachment upon the lumen of the canal may take place without serious pressure upon the cord. Notwithstanding this general anatomical fact, however, correction of bony malalignment and deformity following spinal injury is important and should be performed as soon as it can be properly done.

Typical skeletal deformities of the spine may follow either direct or indirect violence. Direct trauma to the spinal processes and laminae due to blows from the rear in which the laminae are fractured and driven into the bony canal is rare with the closed type of injury, but common with gunshot wounds. When encountered immediate laminectomy with the removal of the offending bone is indicated. This is the only type of spinal injury which offers an absolute indication for an early laminectomy.

Indirect trauma of the spine produces typical deformities. In the cervical spine there usually occurs a forward dislocation of the head and the upper portion of the cervical spine over the lower portion of the cervical spine. This may be unaccompanied by any fracture, but it is usually accompanied by a fracture of one or more of the articulating facets of the affected vertebrae. It should be borne in mind, however, that the essential lesion is usually that of a forward dislocation and that the fracture of the articulating processes is secondary. This typical injury is referred to as a fracture-dislocation.

In the thoracic spine, the splinting afforded by the thoracic cage is so great that fractures severe enough to produce neurological signs rarely occur unless the trauma has been of extreme violence, as when, for example, a person falls from a great height or is thrown from a rapidly moving vehicle against a telegraph pole or tree. Under such circumstances ribs are usually broken, destruction and malalignment of the spinal column are tremendous and the spinal cord is usually transected.

In the lumbar spine following sudden arrest of forward motion of the patient's body, the strong articulations between the vertebrae hold fast, but the bodies of the vertebrae give way. The resulting and typical lesion is a compression of the body of one or more of the lumbar vertebrae usually just below the thoracic cage. Dislocation between the vertebrae either forward or lateral is rare, and acute forward angulation is the main deformity.

The treatment of bony deformities depends upon the nature and site of the injury. Depressed fractures of the laminae require immediate laminectomy and the elevation of depressed bone.

Fracture-dislocation of the cervical spine is best corrected by closed traction methods. Laminectomy, with open operative reduction is usually not only unnecessary but is strongly contraindicated and should not be employed. The best method of reduction is by skeletal traction applied with the "skull tongs" described by Crutchfield. Halter traction with straps applied around the occiput and beneath the chin is unsatisfactory because it is extremely uncomfortable, it interferes with movements of the jaw in eating and talking, and it tends to produce pressure sores beneath the chin and at the occiput. Furthermore, considerably less traction may be applied by this method. The former practice of rapid reduction, using traction of great force, with the immediate application of a plaster cast extending over the occiput and chin down over the thorax, is no longer justifiable with the

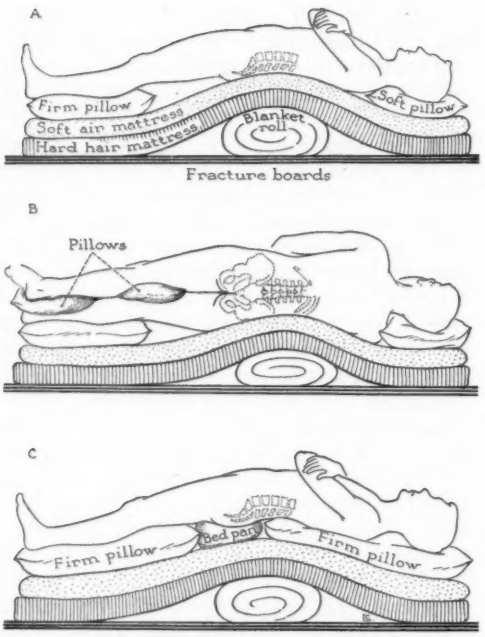

Fig. 2. Care of the patient with compression fracture of the lumbar spine. A, Position of rest. B, Position on the side. C, Method of using bed pan.

newer methods now available. Frequent x-ray examination should be used to control the reduction of the fracture-dislocation at all stages, both early and late. Traction should be maintained until sufficient time has elapsed for firm fibrous union to be established between the injured vertebrae, and this usually requires at least 6 weeks; in severe injuries 12 weeks. Weight-bearing should be deferred until repair of bone is well under way; patients, therefore, should remain in bed, in a prone position, for approximately 12 weeks after removal of traction. When the patient finally becomes ambulatory he should wear a plaster or a leather collar for 6 months or more.

Fractures of the thoracic spine with the usual gross misalignment of the vertebrae cannot be satisfactorily corrected by any method, open or closed. The spinal cord has usually been transected at the time of injury and prognosis for the recovery of spinal puncture is hopeless. Laminectomy is usually futile and hence contraindicated.

Compression fractures of the lumbar spine do not require surgical procedures. Laminectomy is strongly contraindicated in most cases. These deformities are best corrected by closed methods of hyperextension. Fracture boards are first placed upon the bed to prevent sagging. Two or 3 blankets are then made into a roll the width of the bed and approximately 18 inches in diameter. This is placed across the bed on the fracture boards at the level of the spinal injury. A hard, hair mattress is placed over the blanket roll and on top of this a softer mattress, preferably an air-mattress if one is obtainable. The curved surface of the uppermost mattress will then conform approximately to the normal lumbar curvature of the healthy spine. When the fracture bed has thus been set up, the patient is gently lifted on to it, face up, in such a position that the site of the injury lies above the blanket roll. The weight of the upper and lower parts of the body will then serve slowly to bring the kyphosed spine into a position of normal lumbar lordosis. This method of reduction is far more efficient and less traumatizing, mentally and physically, to the patient than is the older method of reduction by suspension upon a canvas hammock (Fig. 2a).

The bed care of patients with fractured spine is of prime importance. In order to change bed linen or to bathe these patients, they may be turned on their side without risk of injury if the bed has been properly set up. The soft tissue between the hip, the pelvis, and the lower edge of the thorax will conform very satisfactorily to the curvature of the bed as the patient is turned without permitting significant lateral misalignment of the spinal column. Moreover, the large intervertebral articulations at the level of the lesion are rarely damaged sufficiently to allow lateral misalignment (Fig. 2 b).

In using the bed pan the patient is rotated gently to one side. The bed pan is then placed in the center of the bed and firm pillows or folded blankets having the same thickness as the bed pan itself, are placed on the bed above and below it. If these pillows or blankets have the correct thickness and firmness and are properly placed, the original curvature of the top mattress is preserved (Fig. 2 c).

The patient is then slowly rotated on to his back so that his back and legs are supported at exactly the same level as the bed pan. In this way hyperextension of the spine is maintained. A bed pan should never be placed beneath a patient with a compression fracture of the lumbar vertebrae unless these precautions against anteflexion are first taken. Another method of evacuating the bowels of a patient with a fractured spine is to place him upon one side and carry out colonic irrigation.

Prevention of hypostatic pneumonia is a major problem during the first days of treatment in all fractures of the spine. In fracture-dislocation of the cervical spine specific injury often occurs to the 4th and 5th cervical segments from which the phrenic nerves innervating the diaphragm take origin. In addition to this, the attendant edema of the cord tends to interfere with the passage of impulses from the respiratory center of the brain to the respiratory musculature of the thorax. For these two reasons respiratory movements are apt to be shallow. Coupled with this is the fact that the patient is lying on his back in which position it is difficult for him to clear his mouth and posterior pharynx of accumulated mucus. Should signs of impending pneumonia appear it is imperative that treatment of the pneumonia take precedence over treatment of the fracture, for the reason that an accurate alignment of spine is of no value if the patient dies of pneumonia. Accordingly any patient threatened with or suffering from pneumonia must be turned from one side to the other every 2 to 3 hours, day and night, to permit free drainage of exudate and mucus from first one half and then the other half of the respiratory tree. All other supportative measures generally employed in the treatment of pneumonia should, of course, be utilized.

In compression fractures of the lumbar spine, pneumonia is caused by a different mechanism. The continued hyperextension of the body causes the rectus muscles of the abdomen to pull upon the lower ribs. An acute traumatic periostitis frequently develops at the point of attachment of the rectus muscles. This may be quite painful and cause involuntary splinting of the lower part of the thoracic cage. This limitation of respiratory movements in the lower lobes of the lungs predisposes to the development of hypostatic pneumonia in much the same way that splinting of muscles after upper abdominal operations does. These patients must be given sufficient morphine during the first few days that they are lying in hyperextension to mask the pain due to the mechanism just described. If this be done promptly and adequately respiratory movements will be inhibited only slightly and the tendency to hypostatic pneumonia greatly reduced. Should pneumonia develop the same general principles regarding its treatment apply in the lumbar fracture as in the cervical fracture.

Abdominal distention may occur during the first few days after an injury of the lower thoracic spine due to interference with the autonomic nervous system. It should be dealt with vigorously along the same lines used in treating paralytic ileus following abdominal operations. Passage of a Miller-Abbott tube into the upper alimentary tract is the best method. Pitressin (1 c.c. ampul) or prostigmine (1 c.c. ampul) may be given intramuscularly. Rectal tubes should be used. Enemas of soap suds or water and glycerine may be tried. Hot stupes to the abdominal wall are often effective. As a rule, distention is rarely critical and is usually short-lived.

All so called "bed sores" are "pressure sores" and are invariably the result of local ischemia caused by continued pressure upon soft tissues. It is no longer permissible to regard pressure sores as "trophic" disturbances. Prevention is the best treatment. This demands constant vigilance to prevent continuing pressure by a hard bed, or by other parts of the body, upon soft tissues overlying bony prominences. Wherever possible a paralyzed patient should be placed upon an air-mattress. As a rule the patient may lie on his back on such a mattress indefinitely without developing pressure sores of the skin over the sacrum. Even with an air-mattress, however, it is necessary to keep the heels off the mattress by placing a firm pillow or a folded blanket of sufficient thickness crosswise beneath the calves of the legs so that the heels do not touch the bed. Small pillows or cotton pads must also be placed between the knees and between

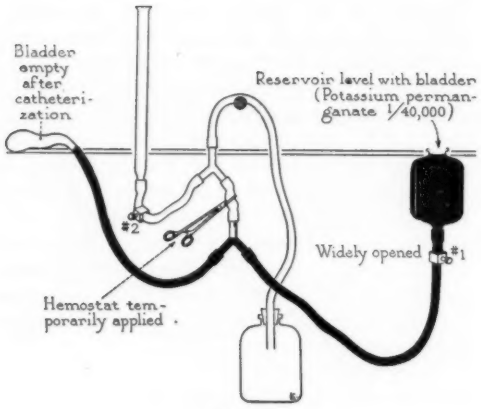

Fig. 3

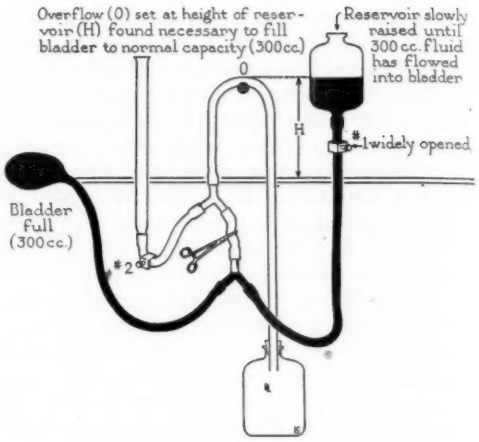
Overflow (O) set at height of reservoir (H) found necessary to fill bladder to normal capacity (300 cc.)
Reservoir slowly raised until 300 cc. fluid has flowed into bladder
O
H
#1 widely opened
Bladder full (300 cc.)
#2

Fig. 4

the ankles and toes. Finally the bed covers must be kept off the toes by means of a frame.

If an air-mattress be not available prevention of pressure sores is very much more difficult. Under these circumstances, air rings, when available, should be used to protect bony prominences. If these be not available, the surgeon must rely upon frequent turning of the patient and the use of cotton pads at vulnerable points to prevent the development of pressure sores.

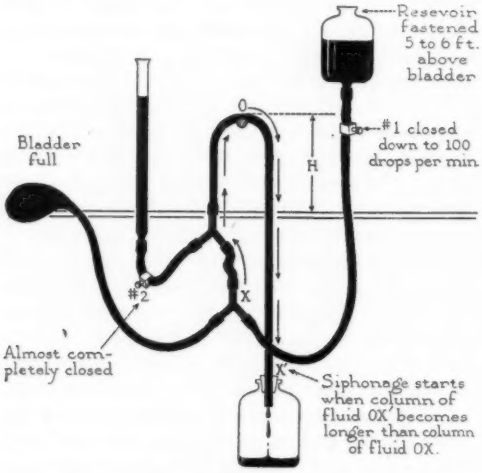
Resevoir fastened 5 to 6 ft. above bladder
O
#1 closed down to 100 drops per min.
Bladder full
H
#2
X
Almost completely closed
X
Siphonage starts when column of fluid OX becomes longer than column of fluid OX.

Fig. 5

The treatment of existing pressure sores should follow the same basic surgical principles applying to the treatment of other wounds containing infected and necrotic tissue. All devitalized skin, fat, and subcutaneous tissue must be excised immediately with scalpel or scissors. Wet saline compresses, Dakin's solution or moist sulfonamide dressings must be applied to the infected base until it is covered by healthy granulations. Skin grafts may be used to hasten healing.

Plaster casts should not be applied to the trunk and extremities of any patient with a spinal injury having anesthetic skin.

Care of the bladder is a major problem in every paralyzed patient. The purposes of treatment are twofold: (a) the prevention of serious sepsis of the urinary tract, and (b) preservation of normal bladder capacity and musculature. The former is necessary for the preservation of life; but the latter is very important if the patient is to make a satisfactory social adjustment after his recovery from the acute phases of his injury. In an effort to attain the former objective, the secondary objective should not be ignored.

Extreme distention of the bladder should be avoided at all times, as a first principle. An in-lying catheter should therefore be introduced at the time emergency treatment is given before distention occurs, and especially before the evacuation of the patient to distant

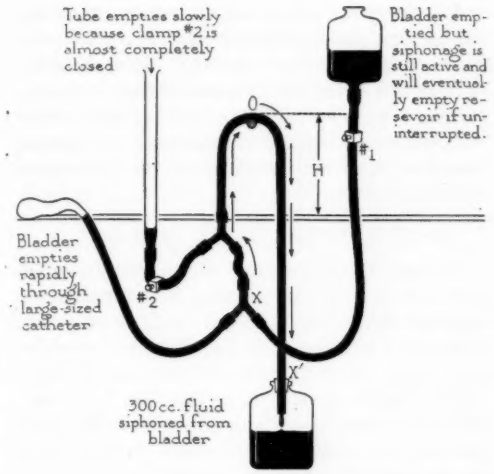
Tube empties slowly because clamp #2 is almost completely closed
Bladder emptied but siphonage is still active and will eventually empty reservoir if uninterrupted.
0
H
#1
Bladder empties rapidly through large-sized catheter
#2
X
X'
300 cc. fluid siphoned from bladder

Fig. 6

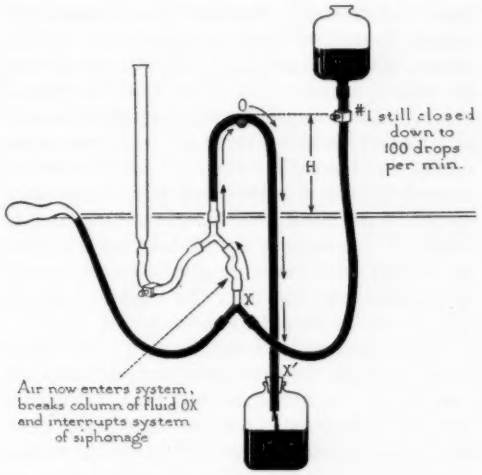
0
#1 still closed down to 100 drops per min.
H
X
X'
Air now enters system, breaks column of fluid OX and interrupts system of siphonage

Fig. 7

points is initiated. If cystitis develops it will not become serious provided drainage be free and the bladder mucous membrane has not been fissured or the muscular walls paralyzed by extreme distention. It can be readily cleared up with the aid of tidal drainage and sulfonamide therapy at the hospital to which the patient has been evacuated. The in-lying catheter should be as large in caliber as the patient will readily tolerate.

Tidal drainage is considered the method of choice in the treatment of the paralyzed bladder and should be instituted as soon as the paralyzed patient is received in an established hospital. Should standard sets not be available at the time needed, the neurosurgeon should improvise tidal drainage along accepted lines. There are several acceptable forms of tidal drainage; one is here shown for purposes of reference (Fig. 3 to 8). It is important that the catheter and drainage tube should be brought out over the thigh, rather than allowed to fall down between the thighs and lie along the bed. In this latter position an acute angulation of the urethra occurs at the level of the suspensory ligament which will contribute seriously toward the production of irritative urethritis. By bringing the tube laterally over the thigh, this angulation with its resultant urethritis is prevented. The in-lying catheter should be removed approximately once a week. This should be done in the morning and a new catheter should not be replaced until late in the day. This allows 8 to 10 hours for voluntary micturition to occur if the bladder mechanism is ready to assume that function. If voluntary micturition does not occur, the catheter should be replaced and tidal drainage continued for another week, when the procedure outlined above should be repeated.

Voluntary control of the bladder often does not return until 6 or 12 weeks after injury,

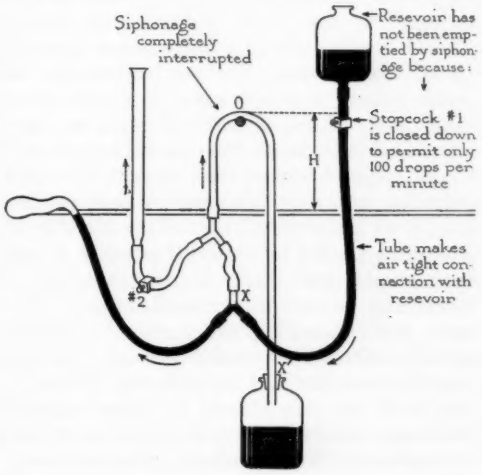

Fig. 8

and tidal drainage should not be discontinued before that time without good and specific cause. Even in cases in which the spinal cord has been completely sectioned at the time of injury, an automatic type of bladder can usually be established after 8 to 12 weeks. After removal of the catheter in such a bladder there is no dribbling of urine; and periodic voidings of 150 to 300 cubic centimeters of urine can be initiated voluntarily by abdominal straining or by sustained pressure applied manually to the abdominal wall over the bladder area by patient or attendant at periodic intervals.

Cystotomy should not be employed when tidal drainage by urethral catheter is available unless that method has been fully tried and proved unsatisfactory. The only absolute medical indication for cystotomy is a fulminating urinary infection which has not responded satisfactorily to tidal drainage. A high cystotomy is preferable to a low one. This procedure should be performed by a urologist if he is available.

Compound injuries of the spine usually result from gunshot wounds and often are associated with penetrating wounds of the thorax or abdomen. Early laminectomy with full exposure of the cord is usually indicated but must be regarded as secondary to the treatment of the thoracic or abdominal wound. Splinters of bone and metal should be removed from the canal when their presence threatens damage to the cord. Sulfonamide powder should not be directly introduced into the spinal fluid or onto the cord, although the small amounts which may get there from other parts of the wound will cause no damage. Disinfection of the cerebrospinal fluid should depend upon a high blood level of sulfadiazine, and with this drug the cerebrospinal fluid level is about half that of the blood level. The dura should be closed if possible to prevent spinal fluid leak. A free transplant of fascia may be used to accomplish this if necessary. Sulfanilamide powder should be lightly sprinkled about the exposed bone, and throughout the muscular and fascial layers. These tissues and the skin should be closed without drainage, otherwise a spinal fluid leak with formation of a fistula and with terminal meningitis is apt to occur.

Recovery of function in extremities and sphincters after severe spinal injury may require weeks or even months. If meticulous care of the skin, bladder and limbs, including massage, passive motion of joints and corrective splinting, be maintained, many seemingly hopeless cases will recover a great measure of useful function.

Peripheral Nerve Injuries

In simple lacerations of soft tissue made with sharp-edged or pointed instruments, peripheral nerves are often divided cleanly with minimal contusion of the nerve trunk on either side of the division and without loss of nerve tissue, either immediate or late. In such cases the two ends of the divided nerve can be easily approximated without tension. Suture of the nerve in this type of injury may be performed at the same time that first surgical care is given to the flesh wound, provided that the wound is fresh, suitable instruments are at hand, time is sufficient and other circumstances favorable.

Accepted surgical principles and technique should be employed in repair of both nerve and flesh wound. Interrupted sutures of fine silk or tantalum wire placed in the epineurium should be used for suture of the nerve. Primary closure of skin is mandatory if suture of the nerve has been performed. Drains are generally undesirable, but if considered temporarily necessary on account of oozing they should never come in contact with the sutureline of the nerve and should be removed during the first 24 hours after operation.

Sulfanilamide powder may be dusted lightly into the wound and about the suture line. This drug increases scar tissue reaction slightly in the soft tissues about the nerve; but does not interfere with the regeneration of the nerve. Evidence is accumulating, however, to indicate that sulfadiazine, given by mouth, in sufficient quantity to maintain a high blood level of the drug affords as great or even greater protection against infection than does sulfanilamide powder placed directly in the wound, without certain undesirable secondary effects caused by the latter procedure.

In the severe, penetrating or crushing wounds commonly encountered in war, in

which major nerves have been divided, definitive suture of these nerves at the time of first surgical care, while theoretically desirable, is almost never feasible. The reasons are as follows: In the first place, in badly contused nerves the full extent of the intrinsic hemorrhage and other damage to the bruised ends of nerves cannot be immediately appraised, nor can the ultimate line of demarcation between viable and nonviable nerve be determined. Second, if much of the nerve has been shot away, reapproximation of the ends of the divided nerve will be possible only if the nerve is "mobilized" for considerable distance on both sides of the injury. To carry such dissection away from a grossly contaminated and potentially infected field, proximally into clean tissues would entail serious and unnecessary risks. Third, proper mobilization and suture of a badly damaged nerve might well require several hours of operating when neither the patient's condition nor the exigencies of the situation would justify the expenditure of so much time. And finally, the surgical necessity of leaving most battle wounds of soft tissue unsutured for 5 to 10 days after initial débridement would almost certainly result in a breaking down of the line of sutures.

In practice, battle wounds usually do not reach the surgeon until 12 to 48 hours after they have been incurred, at which time the first concern is the prevention of sepsis in the soft tissues, especially gas-bacillus infection. This is dependent largely upon proper débridement of the wound. Débridement of the skin should be conservative; but exploration of the wound should be very thorough. The tracts of missiles should, in most instances, be laid open; all foreign matter, such as bits of clothing, should be scrupulously sought out and removed; and all muscle which appears deprived of its blood supply, badly crushed, or grossly contaminated should be excised. The free ends of divided nerves, if these be seen, should be drawn together when possible with several temporary sutures of fine catgut or tantalum wire placed in the epineurium to prevent retraction of the nerve ends pending final definitive suture at a later date. Silk sutures should not be used for this purpose as the silk will remain as infected foreign matter. The wound is not sutured, but merely covered with a protective gauze dressing. It is best not to introduce sulfanilamide powder locally into the wound; but a high "sulfa" level in the blood stream should be early established and maintained by the systemic administration of sulfadiazine.

Secondary closure of the wound may usually be performed 5 to 10 days after débridement. At the time this is done, there should be a therapeutic sulfonamide level in the blood stream. The edges of the skin should again be freshened up, and granulation tissue trimmed away. The skin should then be undermined and mobilized as much as necessary to effect approximation of its edges, and sutured with simple or "vertical" mattress sutures. Moderate tension is well tolerated; and is justified, if necessary, to effect closure. Drains are not needed, and should not be used. Neither sulfanilamide or penicillin should be placed in the wound; but a therapeutic level should be maintained in the blood until the wound has healed. Sutures may be removed, as a rule, after 7 to 10 days; and the wound may be regarded as healed 2 to 3 weeks from the time of operation.

The final definitive suture of the nerve may be performed 2 or 3 weeks after the sutures have been removed. At this time proximal and distal segments of the nerves should be exposed and the ends of the nerves freed from surrounding cicatrix; intrinsic scar tissue excised from the terminal ends of the nerve segments; the nerve trunks "mobilized" as extensively as necessary to obtain approximation of the segments without tension; and end-to-end suture performed. The fundamental requirement for all nerve suture is that it be done without tension. The actual suture should be made with interrupted sutures of fine silk thread or tantalum wire, placed only in the epineurium. Following this, the extremity should be immobilized with neighboring joints in positions of flexion, for approximately 3 weeks. After this, another 3 weeks should be allowed, to get the extremity again extended.

Physical therapy should be instituted about the third week after suture. This should include daily massage, to improve circulation;

passive and active motion to keep joints, tendons and muscles supple; and galvanic stimulation, applied directly to individual denervated muscles, to preserve the contractility of muscle element and to prevent the atrophy of disuse. The minimum effective galvanic stimulation consists of 30 contractions of each paralyzed muscle, repeated three times daily, three days each week. More frequent stimulation is, of course, desirable.

Splints should be used as needed to reenforce weakened or paralyzed muscles and prevent contractures; but these splints should be of such a type as to allow free, voluntary, and passive movements of all joints. If plaster-of-Paris splints are used they should be worn only at night, and left off during the daytime, and the patient encouraged to carry out maximum passive and active movements during his waking hours.

THIOURACIL—ITS USE IN THE PREOPERATIVE TREATMENT OF SEVERE HYPERTHYROIDISM

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EXPERIENCE obtained from the clinical use of thiouracil over a period of 2 years permits certain conclusions regarding this potent biochemical agent. Thiouracil does reduce the elevated metabolic rate of hyperthyroidism to normal if it is administered over a sufficient length of time; in addition there is a gradual disappearance of all hyperthyroid manifestations except those of the eyes if these manifestations are very pronounced before treatment is begun. Conclusive proof has been definitely established that thiouracil possesses great therapeutic value in the preoperative management of severe hyperthyroidism. Consistent and permanent remission of hyperthyroidism by prolonged administration and then withdrawal of thiouracil seems highly unlikely. Considerable time and further careful observations will be required to determine this possibility.

Further comparisons can now be made between the pathologic physiology of the hyperthyroid gland under iodine therapy and that following thiouracil administration. Observations have been made on the thyroid tissue removed at operation from patients receiving thiouracil alone and thiouracil in combination with iodine. An attempt will be made to evaluate the findings.

This report will be discussed under 3 headings: (1) clinical observations, on severely hyperthyroid patients prepared for thyroidectomy with thiouracil; (2) comparison of the action of Lugol's solution with thiouracil on the hyperthyroid gland; and (3) pathologic observations on thyroid tissue removed at operation from patients treated with thiouracil only and thiouracil in combination with Lugol's solution.

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CLINICAL OBSERVATIONS

Thiouracil has been used at the Lahey Clinic in the preoperative management of severely toxic hyperthyroid patients since May, 1943. In dealing with the hyperthyroid patient surgically, we were convinced early that thiouracil is of great advantage since it has the power to bring about a positive remission in patients who are dangerous risks or who are so toxic as possibly to require multiple stage procedures. In addition to eliminating two stage thyroidectomies entirely, deaths which result from so called postoperative thyroid storm or reactions are avoided with certainty. Patients with mild hyperthyroidism continue to be prepared with iodine since in this group sufficient improvement occurs to permit thyroidectomy without risk and the dangers entailed with the use of thiouracil are thereby avoided.

One hundred ninety patients with severe hyperthyroidism have now been treated preoperatively with thiouracil and have gone through thyroidectomy. Both types of hyperthyroidism were represented in this group—primary hyperthyroidism, or Graves' disease, and adenomatous goiter with hyperthyroidism. Response to thiouracil therapy was equally satisfactory in the two groups. When treatment was continued sufficiently long, no patient failed to respond satisfactorily.

In the first 100 patients treated, there were 85 females and 15 males. The age varied from 11 to 77 years; the average age was 45 years. Forty-four patients were over 50 years of age. The average duration of the hyperthyroidism was 24 months. Almost half, 43 patients, had had hyperthyroidism for more than 2 years; of these, 11 had been ill for more than 5 years. Twenty-five of the 100 patients had lost more than 40 pounds, average weight loss being 25 pounds. The average basal metabolic rate was +49; 54 patients had initial rates over +45.

All of the patients were considered to have severe hyperthyroidism since most were in the older age group, the disease was usually of long duration, considerable weight loss had occurred, and the basal metabolic rates were usually high. Thirty-five of the 190 patients were classified as thyrocardiacs, having either heart failure or auricular fibrillation without heart failure. This latter group of patients in our experience has in the past carried the highest mortality rates following thyroid surgery.

PLAN OF TREATMENT

For most patients treatment is ambulatory. Those with hyperthyroidism and associated heart failure or those extremely ill from hyperthyroidism alone are admitted to the hospital. In the former group, combined cardiac and thiouracil treatment is begun, and when cardiac compensation is restored after 10 to 14 days, these patients are discharged to carry on treatment at home. In the latter group improvement is usually sufficient after 7 to 10 days to permit continuance of treatment at home. Patients are advised to eat a high calorie diet, three full meals a day with lunches between meals. Physical activity is slowly increased as the improvement in each patient's condition seems to warrant it; some patients have been confined to bed for as long as 2 to 3 weeks at the beginning of treatment. All patients, those hospitalized and then discharged and those not hospitalized, are seen every 10 days to 2 weeks at the clinic or by the referring physician for routine examination and white and differential blood counts. If suspicious change in the blood is observed or any other toxic manifestation is suggested, the patient is seen more often. Patients are advised as to possible toxic reactions and told to call their physician at once if any should occur.

Thiouracil is administered in a total daily dose of 0.6 gram, 0.2 gram, at 7 a.m., 2 p.m., and 9 p.m. This full dose is continued until the maximum benefit is obtained. At this point all hyperthyroid manifestations will have subsided, with the basal metabolic rate being normal. The objection to reducing the dose of thiouracil as improvement occurs is that the duration of treatment may be prolonged and if the dose is reduced too rapidly, the symptoms may actually increase under treatment. Also, discontinuing the thiouracil too long before thyroidectomy may permit an increase in hyperthyroidism. Our early experience with the use of thiouracil taught us that thyroidectomy should not be performed before optimum improvement is obtained, since short of this an unsatisfactory course under anesthesia and alarming postoperative reaction may occur, thereby mitigating the complete benefit of preoperative thiouracil therapy.

The time required to accomplish the desirable degree of improvement necessary to permit safe thyroidectomy is determined fairly accurately from the height of the basal metabolic rate. It has been found that approximately one day of treatment with 0.6 gram of thiouracil is required for each percentage of elevation in the basal metabolic rate. For example, a patient with a basal metabolic rate of +55 will require approximately 55 days of thiouracil therapy to bring the basal metabolic rate to normal. Those patients who have received Lugol's solution before the administration of thiouracil responded less quickly and usually required a slightly longer period of treatment to return the metabolic rate to normal. Those patients who had had hyperthyroidism of short duration, 2 to 3 months, responded more quickly to treatment than did those who had had the disease a longer time. Those patients with very large glands responded more slowly, but on the whole the size of the gland did not seem to be an important factor in the time necessary to reduce the metabolic rate to normal. With this knowledge individualizing the treatment of each patient, the date of readiness for operation can be accurately estimated and hospital arrangements can be made far in advance. There was no patient who was "thiouracil-resistant" and in no case was there failure to bring the basal metabolic rate to normal if treatment was continued sufficiently long.

The average initial basal metabolic rate of the first 100 patients having thyroidectomy was +49. After an average of 57 days of treatment, the average basal rate was +7.

Three patients received thiouracil for over 100 days and 59 patients for over 50 days. The average gain in weight was 12 pounds, with 19 patients gaining over 20 pounds.

Surgical procedures. Of the total 190 patients, 177 were subjected to subtotal thyroidectomy and 14 patients had hemithyroidectomy. Of these latter 14 patients, 4 had very large goiters and it was thought at the time of operation unwise to do a subtotal thyroidectomy. These patients were treated early in our experience before the smooth anesthesia and postoperative course of patients treated adequately with thiouracil had been observed. Since thyroid toxicity is absent the time factor in the operation is no longer important, so extremely large glands are now removed at one stage. Four patients were not treated long enough with thiouracil to permit subtotal thyroidectomy without risk, as indicated by an unsatisfactory anesthesia course. These cases also occurred early in our experience before optimum improvement prior to operation was thought essential. Five patients were prepared with thiouracil for second stage thyroidectomy, the first stage having been performed following iodine preparation. One patient had only a hemithyroidectomy because of the extreme technical difficulty in removing a recurrent goiter. There were no postoperative deaths.

When the first patients receiving thiouracil underwent thyroidectomy a most unsatisfactory surgical complication was encountered. The thyroid gland was found to be soft and friable, and bleeding of the entire operative site was so extensive that there was difficulty in keeping the field sufficiently dry to carry out the usual desired surgical technique, including the isolation of the parathyroid glands and the recurrent laryngeal nerves. Since 24,000 patients with goiter have been operated upon in the surgical department of the clinic, all of the surgeons are familiar with all of the technical difficulties which may arise while doing a subtotal thyroidectomy in hyperthyroidism. If they complain of really distressing technical difficulties in operating upon those patients who have been prepared solely with thiouracil, it must be assumed that these technical difficulties are really of serious character and in no way imaginary. Hemostats, double hooks, or even ligatures fail to hold or pull out on the slightest traction. Oozing is almost ceaseless and is controlled only with the greatest patience and difficulty. It was also often impossible to do as radical a thyroidectomy as is desirable. After suffering through a number of these operations it was the opinion of the operating staff that the desirable effect of thiouracil upon the basal metabolic rate was being considerably offset by the undesirable difficulties entailed in carrying out the subtotal thyroidectomy.

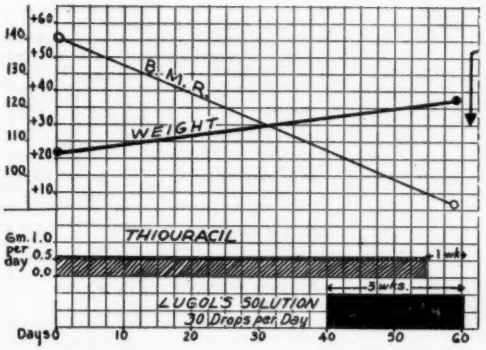

Fig. 1. Illustrative case, showing combined use of thiouracil and iodine in preoperative management of hyperthyroidism; also duration of treatment in comparison to height of initial basal metabolic rate. Arrow indicates subtotal thyroidectomy. Mrs. A. E., aged 53 years, severe primary hyperthyroidism. Gland was 5 to 6 times normal size; pathologically it showed early involution.

The friability of the thyroid gland was overcome when Lugol's solution was administered during the 3 week period immediately before operation. For 2 weeks the iodine and thiouracil are administered simultaneously and during one week preoperatively the thiouracil is discontinued and only iodine is administered. The thiouracil is discontinued 1 week before operation since it has been determined that the basal metabolic rate continues to drop even though the thiouracil is stopped. It is also suspected that involution is furthered when thiouracil is not being administered. Also, the danger of possible toxic reactions from the drug developing at the time of operation is avoided by this plan. The supplementary use of iodine preoperatively is not required in patients with adeno-

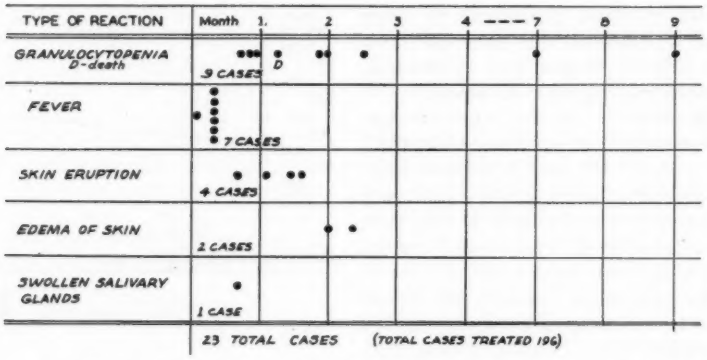

Fig. 2. Types of reactions from thiouracil therapy. Onset of reactions is shown in relation to duration of treatment.

matous goiters since this type of gland is not altered by thiouracil therapy.

An example of the combined use of thiouracil is given in Figure 1. In this typical case with severe hyperthyroidism with a basal metabolic rate of +55, 0.6 gram of thiouracil was given daily for 54 days, its administration was discontinued 1 week before operation, and Lugol's solution was given daily during the 3 week preoperative period. The basal rate before operation was +6. The iodine given preoperatively produced firmness of the gland, the palpable thrills and bruits became less marked, and at operation the thyroid was sufficiently firm so that no technical difficulty was encountered.

In patients adequately treated with thiouracil, the pulse remains constant during anesthesia, as does the blood pressure, in contrast to the rising pulse rate and blood pressure in patients treated preoperatively with Lugol's solution alone. No evidence of toxicity is observed, the anesthesia course being that seen during the removal of a nontoxic adenomatous goiter. The postoperative course is also free of reaction. The worry and concern over postoperative reactions have now been entirely eliminated. The intensive use of sedation, intravenous fluid, and oxygen administration postoperatively is no longer necessary. Because of these changes, a revision of postoperative treatment after thyroidectomy has become necessary. Overtreatment with thiouracil which produces a myxedematous state must be avoided since patients with myxedema are extremely sensitive to anesthesia and preoperative and postoperative sedation. When patients are myxedematous, even small doses of sedation may suppress the respiration and with the usual presence of mucus, may lead to pulmonary complications.

TOXIC REACTIONS DUE TO THIOURACIL

Toxic manifestations (Fig. 2) developed in 23 patients[1] receiving thiouracil, 18 of these being in the aforementioned group operated upon. The reactions consisted of granulocytopenia, 9 patients; fever reactions, 7 patients; skin eruption, 4 patients; scleredema, 2 patients; and swelling of the salivary glands, 1 patient.

Leucopenia with granulocytopenia is the most serious and alarming of all the reactions to thiouracil. The blood changes in the 9 cases occurred as early as 25 days and as late as the 9th month, the dose of thiouracil varying from 0.6 to 0.05 gram daily. The changes in the blood usually occurred quite suddenly, with a reduction in the total white count and in the percentage of polymorphonuclear cells. The total white counts in this group were 4300, 4200, 4000, 3800, 3850, 2400, 1600, 1000, 900, with the respective polymorphonuclear count being 12 per cent, 45 per cent, 12 per cent, 23 per cent, 34 per cent, 36 per cent, 6 per cent, 0 and 0 per cent, not a proportionate

[1]Twenty-three (11 per cent) of a total of 196 patients who were given thiouracil during that time.

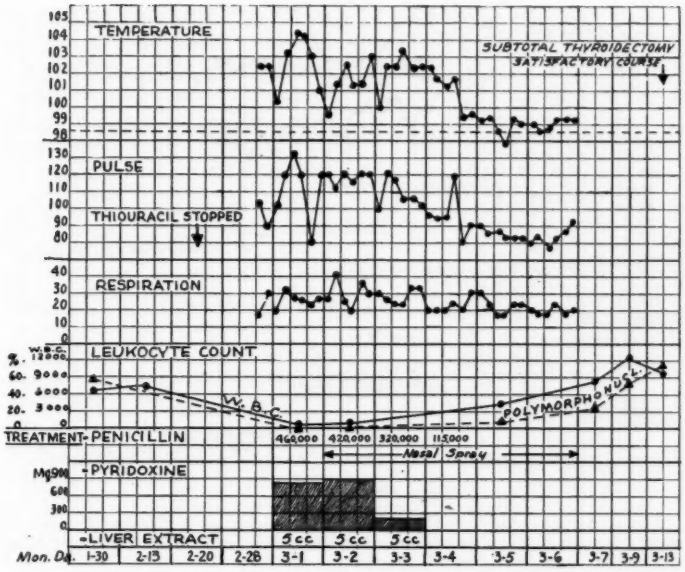

Fig. 3. Agranulocytosis with severe clinical manifestations developing 8 days after discontinuing thiouracil. Improvement occurred after intensive treatment. (Penicillin thought to be the most beneficial part of treatment.) Mrs. S. K., aged 36 years, severe primary hyperplasia of 2 years' duration. Weight loss 165 to 105 pounds; basal metabolic rate, initial +85, final +26; pulse, 140. Thiouracil, 0.6 gram daily for 75 days. Gained 11 pounds.

drop. Four patients developed the clinical picture of agranulocytic angina, 2 mild and 2 severe; 1 of the latter patients died.

This patient, a woman of 41 years with severe primary hyperthyroidism, had received thiouracil, 0.6 gram daily, for 37 days when she developed a mild sore throat. A blood count one week before showed a total white count of 5000 with 70 per cent polymorphonuclear cells. The thiouracil was discontinued when the sore throat began and symptomatic treatment was advised. Five days later she was admitted to the hospital in the city where she resided, because the throat symptoms had progressed. The temperature at this time was 105 degrees. The white count was 1000 and no polymorphonuclear cells were seen in the smear. Four hundred thousand units of penicillin with adequate fluid were immediately given intravenously, but death occurred after 8 hours.

Since that experience, a second case with severe granulocytopenia has been observed.

Fever and throat symptoms developed 8 days after discontinuing thiouracil. The total white count was 900, with no polymorphonuclear cells in the differential smear (Fig. 3). Treatment consisted of large doses of penicillin intravenously and intramuscularly and by nasal and throat spray, pyridoxine,[1] and crude liver extract. In 48 hours there was a decided improvement in the patient's clinical condition. In 10 days the white blood count had returned to normal and the patient had a subtotal thyroidectomy without reaction.

One patient with mild beginning agranulocytic angina (Fig. 4), having only a slight systemic reaction, also responded equally well to treatment with penicillin, pyridoxine, and folic acid. One patient had mild symptoms and recovered without treatment. The other patients who had blood changes were asymptomatic and following the discontinuance of thiouracil, the white blood cells returned to normal within 7 to 10 days.

This experience with the blood changes during thiouracil administration shows that the changes may occur at any time during therapy and that agranulocytosis may develop even as long as 1 week after treatment is stopped. There is no relationship between

[1]Given on the basis of the work of Max M. Cantor and J. W. Scott, of the University of Alberta. Canad. M. Ass. J., 1945, 52: 368–371.

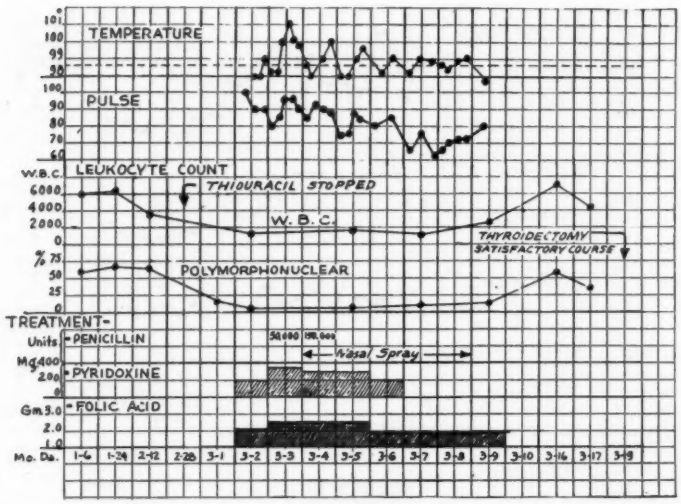

Fig. 4. Agranulocytosis, with mild clinical manifestations. Mrs. M. W., aged 61 years. Adenomatous goiter with hyperthyroidism. Thyrocardiac. Basal metabolic rate, initial +43, final +19. Thiouracil 56 days.

the dose used and the possibility of a fatality. This makes frequent blood studies essential during treatment, and careful observation and intensive therapy are necessary if agranulocytic angina occurs. Although we used other substances in the treatment of patients with agranulocytic angina, penicillin was unquestionably the potent and most beneficial agent, producing recovery in the 2 patients under our care. This conclusion seems justified since it was observed that clinical improvement resulting from sterilization of the body occurred before blood changes were noted. Studies aimed at preventing the blood changes are now under way since prevention of blood changes seems essential before free use of thiouracil will be safe.

Fever with severe generalized muscular aching and pain, especially in the upper back and neck, occurred in 7 patients. A fever of 103 degrees developed on the tenth day in 6 patients. In each of these patients the fever subsided promptly on the discontinuance of thiouracil and when 0.1 gram of thiouracil was again administered, a fever response, with a return of muscular pain, took place in 2 to 3 hours. One patient developed fever on the second day of treatment; she also had a return of symptoms, chills, fever and nausea, when a repeat dose of 0.1 gram was given. Four of these 7 patients who developed fever were then placed on thiobarbital, 0.2 gram per day. Three of the 4 continued taking this substance until full control of hyperthyroidism was accomplished, at which time a subtotal thyroidectomy was done. The fourth patient developed both fever and leucopenia following the administration of thiobarbital so that the treatment had to be discontinued. Further preoperative treatment in this case was carried out with Lugol's solution.

Four patients developed a severe, pruritic skin rash during treatment. The rash was maculopapular in type and fairly well generalized, but was particularly noticeable on the arms and around the neck. It occurred on the 21st, 34th, 44th, and 48th day of treatment. In 2 cases the drug was discontinued with prompt relief of symptoms. In both of these patients the hyperthyroidism was well controlled so that thyroidectomy was done without delay. In 2 patients the hyperthyroidism was severe enough to require further treatment. In both of these the dose of thiouracil was cut to 0.3 gram a day, and local skin treatment was given. The skin im-

proved so that sufficient control of the hyperthyroidism could be accomplished to permit thyroidectomy without reaction. This latter experience in reducing the dose of thiouracil with resulting improvement in the skin needs further certification before this plan can be considered as the solution to the troublesome skin reaction.

In 2 patients scleredema or early scleroderma-like changes were noted. Both patients spoke of feeling muscle bound, with the skin feeling tight. This was noted chiefly in the face, hands and upper arms where the skin was found to have lost its normal elasticity. This change occurred after 66 and 70 days of treatment. In 1, the basal metabolic rate was −5 and −6 per cent, with the serum cholesterol 203 milligrams per 100 cubic centimeters, and in the second case, −21 per cent, with the serum cholesterol 276 milligrams per 100 cubic centimeters. The latter patient was in a mild myxedematous state as indicated by the basal metabolic rate and cholesterol determination. Neither patient showed the clinical picture of myxedema, such as dry skin and swollen lids. A biopsy of the skin from the shoulder area in the second patient showed slight edema of the collagen fibers. In both, the skin condition disappeared on stopping the medication; thyroidectomy was done even before the skin had returned to normal. Excess serum accumulation in the wound postoperatively was noted in these patients.

The twenty-third reaction consisted of marked swelling of the salivary glands. This took place on the 23d day of treatment, disappeared a few days after stopping treatment, and quickly returned after 0.1 gram of thiouracil was given. The swelling was not painful and was only troublesome in preventing proper opening of the mouth. The patient was then given thiobarbital without toxic effect until optimum control permitting thyroidectomy was obtained.

These 23 reactions occurred in a total of 196 patients to whom thiouracil was administered, or 11.7 per cent, as compared with 78 (19 per cent) reactions in a group of 405 cases taken from the literature (2). The blood changes, most serious of all reactions leading

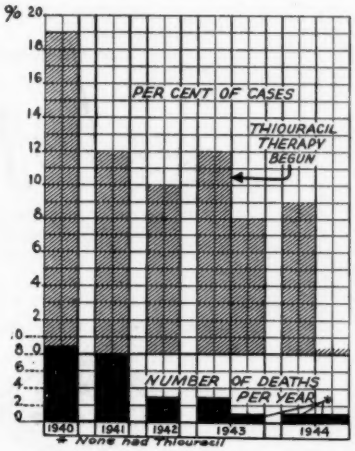

Fig. 5. Drop in the percentage of stage thyroidectomies and postoperative deaths following institution of preoperative treatment with thiouracil.

to possible death, occurred irrespective of duration of administration or dose of thiouracil given. The fever reactions, except in 1 case, occurred on the 10th day of treatment and returned when a small dose was repeated. The skin eruption was variable in its occurrence, from 21 to 48 days. In 2 patients, reducing the dose by 50 per cent permitted continuance of treatment. The edema of the skin occurred fairly late in treatment when the metabolic rate was normal or the patient was in a mild myxedematous state. Swelling of the salivary glands on the 21st day was noted in only 1 case.

The reactions may be considered to have different mechanisms: (a) Blood changes and skin eruption are on a toxic basis; (b) fever and swelling of salivary glands are due to sensitivity; (c) edema of skin results from metabolic disturbance in the skin and subcutaneous tissue.

The use of thiouracil in the management of hyperthyroidism has permitted a great saving of life since thyroidectomy can now be done without risk. In the last 2 years since the introduction of thiouracil there have been 3 postoperative deaths. These patients were not given thiouracil but if it had been given, their deaths could probably have been prevented. When it is remembered that the

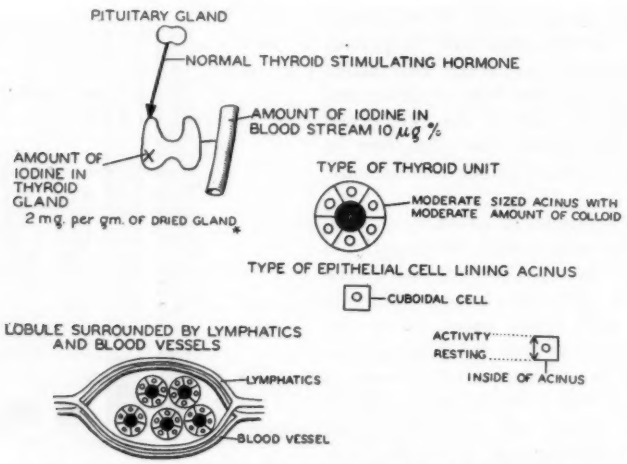
PITUITARY GLAND
NORMAL THYROID STIMULATING HORMONE
AMOUNT OF IODINE IN BLOOD STREAM 10 μg %
AMOUNT OF IODINE IN THYROID GLAND
2 mg. per gm. OF DRIED GLAND
TYPE OF THYROID UNIT
MODERATE SIZED ACINUS WITH MODERATE AMOUNT OF COLLOID
TYPE OF EPITHELIAL CELL LINING ACINUS
CUBOIDAL CELL
LOBULE SURROUNDED BY LYMPHATICS AND BLOOD VESSELS
LYMPHATICS
BLOOD VESSEL
ACTIVITY
RESTING
INSIDE OF ACINUS

Fig. 6. Diagrammatic outline of the normal thyroid physiology.

thiouracil treated patients were all severely toxic and represented serious surgical risks, the value of thiouracil can truly be appreciated. Since the introduction of thiouracil two stage procedures have fallen from the usual 10 to 12 per cent to 3 per cent (Fig. 5). No more two stage operations need be done except for technical reasons. In addition to the lessening of postoperative deaths and the reduction in multiple stage operations, a great economic saving was possible in the group of hyperthyroid patients treated since the hospital stay now is 7 to 10 days as compared with weeks when patients were prepared with Lugol's solution, and the expense of multiple operations is also eliminated.

COMPARISON OF LUGOL'S SOLUTION WITH THIOURACIL ON THYROID GLAND

Before an approach is made to an explanation of the action of thiouracil and to the combined effects of thiouracil and iodine upon the thyroid gland, it may be of interest to discuss a few of the fundamental features of iodine effect upon the thyroid gland as related to its vascularity and friability. These include the effects of iodine upon the histology of the thyroid gland, upon metabolism and upon blood iodine as shown by blood iodine studies. An attempt can be made to explain how thiouracil operates, how iodine functions, the relation of iodine to thyroxin, what involution of the thyroid is and how desirable it is to obtain the combined effects of thiouracil and iodine in the patients with hyperthyroidism coming to operation.

If we assume that the present conception of hyperthyroidism is sound, it is possible to illustrate diagrammatically hyperthyroidism with only one factor missing, that is what incites the excess of the pituitary thyroid stimulating factor. It can be shown that as the result of overstimulation of the thyroid there is resulting hyperplasia, and that as the result of this stimulation and hyperplasia there is a greater production of thyroid secretion which brings about hyperthyroidism with such dramatic clinical evidence of its effect upon body metabolism.

a. Normal thyroid physiology is schematically indicated in Figure 6. The thyroid gland receives stimulation from the thyroid stimulating hormone from the pituitary gland and iodine is taken from the blood stream for the production of thyroid hormone. The normal gland contains 2 milligrams of iodine per gram of dried gland and in the blood at this time there is only 10 micrograms per cent of iodine. The thyroid gland structure has as a unit an acinus which is lined with cuboidal cells. The acinus contains a moderate amount of well-staining colloid, the latter representing

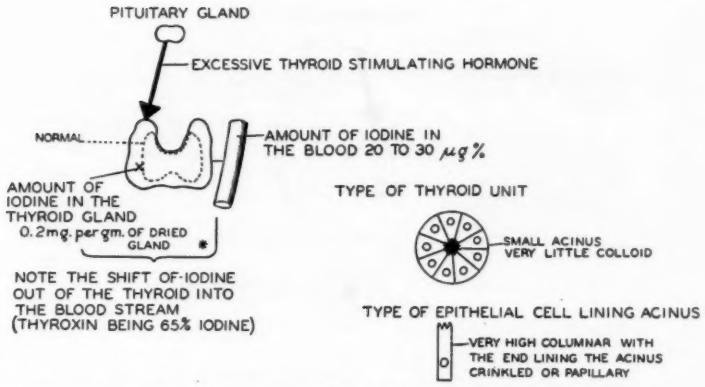
PITUITARY GLAND
EXCESSIVE THYROID STIMULATING HORMONE
NORMAL
AMOUNT OF IODINE IN THE BLOOD 20 TO 30 μg%
AMOUNT OF IODINE IN THE THYROID GLAND
0.2mg. per gm. OF DRIED GLAND
NOTE THE SHIFT OF IODINE OUT OF THE THYROID INTO THE BLOOD STREAM (THYROXIN BEING 65% IODINE)
TYPE OF THYROID UNIT
SMALL ACINUS VERY LITTLE COLLOID
TYPE OF EPITHELIAL CELL LINING ACINUS
VERY HIGH COLUMNAR WITH THE END LINING THE ACINUS CRINKLED OR PAPILLARY

Fig. 7. Diagrammatic outline of the pathologic physiology in primary hyperthyroidism.

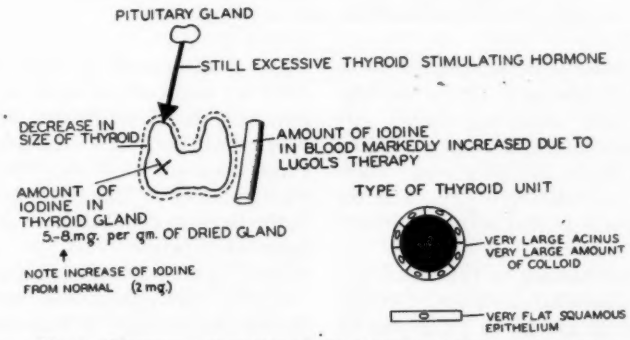
PITUITARY GLAND
STILL EXCESSIVE THYROID STIMULATING HORMONE
DECREASE IN SIZE OF THYROID
AMOUNT OF IODINE IN BLOOD MARKEDLY INCREASED DUE TO LUGOL'S THERAPY
AMOUNT OF IODINE IN THYROID GLAND
5-8 mg. per gm. OF DRIED GLAND
NOTE INCREASE OF IODINE FROM NORMAL (2 mg.)
TYPE OF THYROID UNIT
VERY LARGE ACINUS VERY LARGE AMOUNT OF COLLOID
VERY FLAT SQUAMOUS EPITHELIUM

Fig. 8. Diagrammatic outline of the altered pathologic physiology in primary hyperthyroidism following administration of Lugol's solution.

the normal stored thyroid hormone. The acini are grouped, forming a lobule which is surrounded by blood vessels and lymphatics. Movement of thyroid hormone to the body and manufacture of hormone with storage as colloid is dependent on the body's varying requirement for hormone.

b. When hyperthyroidism with its typical hyperplasia occurs it can be shown diagrammatically, as in Figure 7. An excess of thyroid stimulating hormone causes an overactivity of the thyroid gland due to hyperplasia of the thyroid cells with increased vascularity. The lining cells of an acinus of the hyperplastic thyroid are high columnar, loosely packed, with crinkled edges bulging into the acinus. This type of hyperplastic thyroid gland is friable and bleeds profusely. A shift takes place in the iodine from the gland to the blood stream, with the thyroid containing one-tenth of the usual content of iodine and the blood stream two to three times its normal content.

c. Involution of the hyperplastic hyperthyroid gland can be accomplished by the administration of Lugol's solution (Fig. 8). There is still an excess of thyroid stimulating hormone. The thyroid cell reverts to an inactive phase, becoming flat and compact, appearing to be compressed by the large amount of colloid stored in the acinus. Iodine is increased in the gland up to 5 to 8 milligrams per gram of dried gland. It is this type of acinar distention with a lessened need for an increased blood supply that makes the hyperplastic thyroid become firm so that it is no longer friable. This reduction in vas-

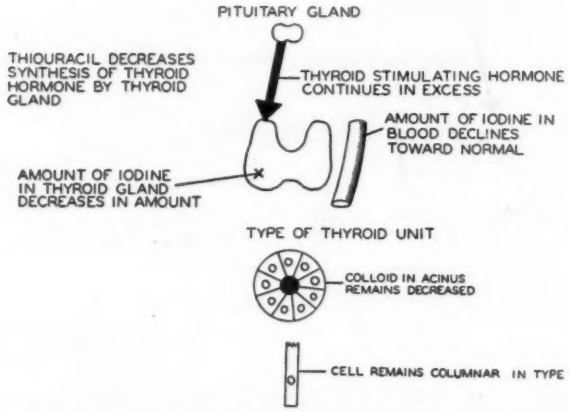
PITUITARY GLAND
THIOURACIL DECREASES SYNTHESIS OF THYROID HORMONE BY THYROID GLAND
THYROID STIMULATING HORMONE CONTINUES IN EXCESS
AMOUNT OF IODINE IN BLOOD DECLINES TOWARD NORMAL
AMOUNT OF IODINE IN THYROID GLAND DECREASES IN AMOUNT
TYPE OF THYROID UNIT
COLLOID IN ACINUS REMAINS DECREASED
CELL REMAINS COLUMNAR IN TYPE

Fig. 9. Diagrammatic outline of the altered pathologic physiology in primary hyperthyroidism following thiouracil administration.

cularity of the thyroid is demonstrated by a lessening of the thrills and bruits at the superior thyroid pole following iodine administration. At operation, a properly iodinized gland shows little bleeding and, when incised, is pale and relatively dry, and on section the dilated acini filled with colloid are readily seen.

d. The exact mechanism of thiouracil action still remains somewhat in doubt. Certain studies suggest its action to be as shown in Figure 9. The pituitary stimulation continues to remain in excess. A disturbance in the synthesis of the thyroid hormone takes place and coincident with this there is a decrease in the iodine content of the thyroid gland. A reduction in the blood iodine occurs and the blood iodine level gradually returns to normal as the basal metabolic rate falls. If thiouracil therapy is continued sufficiently long, a normal blood iodine content is finally reached. The thyroid cell still shows evidence of hyperplasia as during active clinical hyperthyroidism. This continued hyperplastic state of the thyroid following thiouracil treatment accounts for the increased vascularity of the gland. Bruits and thrills are present at the superior poles, together with softness of the gland, and at operation excessive bleeding causes technical difficulty. If the thyroid gland is in a high state of hyperplasia at the time thiouracil treatment is begun, the hyperplasia is increased, as noted by the development of marked softness of the gland. If, however, the gland is firm, spontaneously involuted at the time of starting treatment, the gland does not seem to undergo great hyperplastic change. Therefore, the clinical status of the thyroid gland following thiouracil treatment is dependent on the condition of the gland when treatment is begun.

e. The fifth comparative step in the altered thyroid physiology is that which occurs following the use of combined thiouracil and iodine in preparation of the thyroid gland for its removal. Since thiouracil tends to produce a highly vascular gland, an attempt at preventing this was made by a combination of thiouracil and iodine administration. Thiouracil was begun and continued up to 1 week before operation, with iodine being administered with thiouracil during the last 2 weeks of its use and alone for 1 week before thyroidectomy (Fig. 1). Clinically, a substantial improvement in the gland occurred—the bruits and thrills lessened, the gland seemed to be reduced in size and at operation the thyroid was adequately involuted, it was not friable and bleeding could easily be controlled.

Diagrammatically (Fig. 10), the pituitary stimulation is apparently still in excess with thiouracil decreasing the synthesis of thyroid hormone. The thyroid gland is still able to take up iodine when given as Lugol's solution,

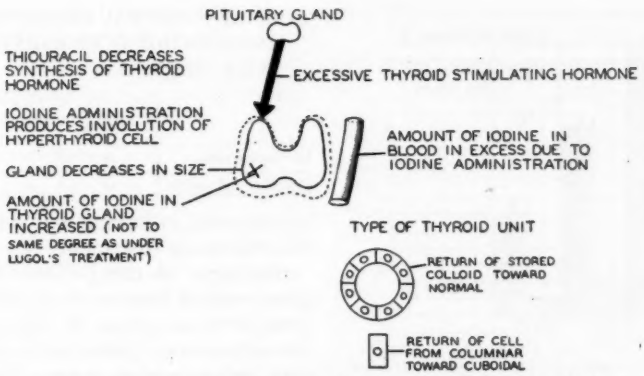
PITUITARY GLAND
THIOURACIL DECREASES SYNTHESIS OF THYROID HORMONE
EXCESSIVE THYROID STIMULATING HORMONE
IODINE ADMINISTRATION PRODUCES INVOLUTION OF HYPERTHYROID CELL
AMOUNT OF IODINE IN BLOOD IN EXCESS DUE TO IODINE ADMINISTRATION
GLAND DECREASES IN SIZE
AMOUNT OF IODINE IN THYROID GLAND INCREASED (NOT TO SAME DEGREE AS UNDER LUGOL'S TREATMENT)
TYPE OF THYROID UNIT
RETURN OF STORED COLLOID TOWARD NORMAL
RETURN OF CELL FROM COLUMNAR TOWARD CUBOIDAL

Fig. 10. Diagrammatic outline of the altered pathologic physiology in primary hyperthyroidism following combined use of thiouracil and iodine.

producing involution, there being no complete block to iodine absorption. The gland seems to decrease in size and becomes firm, with lessening of the bruits and thrills at the superior poles. Iodine, however, must be administered before myxedematous levels are reached since absorption does not seem to take place at that stage of metabolism. The iodine content of the thyroid tissue removed at operation is found to be greater following combined thiouracil and iodine treatment than following thiouracil therapy alone (Fig. 2). An excess of iodine occurs in the blood as a result of iodine administration. Histologically, a tendency to involution occurs but not to the degree seen with iodine treatment alone.

PATHOLOGIC OBSERVATIONS ON THYROID TISSUE AFTER THIOURACIL ONLY AND AFTER THIOURACIL AND LUGOL'S SOLUTION

A careful pathologic study of thyroid tissue removed at operation was carried out on 77 specimens. These patients were among the first 100 treated and include those patients treated with thiouracil alone and those receiving the combined iodine and thiouracil management.

Particular attention was directed to the state of involution of the gland. For a number of years we have classified the degree of involution on the basis of microscopic findings, dividing it into three stages: early involution, when the epithelium is still columnar and the colloid scanty and papillary projections present; moderate involution, when the epithelium is cuboidal, the colloid moderate in amount and papillary projections not frequent; late involution when the epithelium is low cuboidal or flat, colloid fills the acini and is usually fairly dense and homogeneous, and the papillary projections are vestigial. At times, instead of each acinus involuting more or less at an equal rate, there is a mixture of the three preceding stages; this is designated irregular involution. Some glands, usually those with late involution, may show foci, which we classify as hyperinvolution, when the picture almost resembles that of a colloid goiter with flat epithelium and distended acini containing much colloid; the acini remain less than a low power microscopic field in diameter as a rule; the fibrous stroma is not as abundant as seen in a colloid goiter nor does it become loose and edematous as is so often the case in a colloid goiter.

Varying degrees of involution may occur spontaneously in hyperplastic thyroid glands as a result of the diminution of blood supply, as through pole ligation, as a result of removal of a portion of the thyroid, as a result of radiation, or as a result of iodine administration. By examination of involuted glands, it is not possible to state by what means the involution has occurred.

Fibrosis and lymphocytic infiltration are not essential features of involution nor of the effect of iodine or other substances admin-

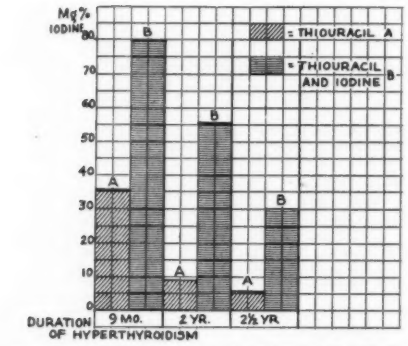

Fig. 11. Comparative cases of primary hyperthyroidism showing iodine content of the thyroid gland following thiouracil therapy alone and following combined use of thiouracil and iodine.

istered but depend more on the age of the patient, the length of time that the gland has been hyperplastic, and, in the case of lymphoid infiltration, whether or not there exists general lymphoid hyperplasia in the patient as so often occurs with hyperthyroidism.

MATERIAL AND METHOD

Of the 77 cases in the thiouracil-treated group (Table I), 47 were classified pathologically as primary hyperplasia and 30 as secondary hyperplasia. In the few instances in which a two stage operation was performed, the second stage specimen was not included in the total.[1] Twelve patients were treated with thiouracil alone; 13 had iodine only before the thiouracil therapy was started. The remaining patients all had iodine preoperatively, 21 having had iodine also prior to the thiouracil treatment.

TABLE I.—TYPES OF GLAND AND TREATMENT

	Thiouracil only	Thiouracil and previous iodine	Thiouracil and preoperative iodine	Thiouracil and previous and preoperative iodine	Total
Primary	5	8	20	14	47
Multiple colloid adenomatous goiter	7	5	11	7	30
Total	12	13	31	21	77

[1]Our experience with glands removed in two or more stages in the "pre-iodine" period of therapy demonstrated that involutional changes may be brought about by removal of a portion of the thyroid alone; therefore, it was impossible to evaluate the changes encountered in the second stage specimens in this group of cases since there were insufficient cases to permit distinguishing between possible thiouracil effect of the previous removal itself.

TABLE II.—STROMAL INCREASE AND LYMPHOID INFILTRATION IN PRIMARY GLANDS TREATED WITH THIOURACIL

	0 or negligible	Slight	Moderate	Marked
Increased stroma	18	25	4	0
Lymphoid infiltration	11	26	9	1

The ages of the patients in the primary group varied from 12 to 77 years, 53 per cent being over 40 years. In the secondary group the ages varied from 14 to 72 years, 77 per cent being over 40 years. Six of the former group and 5 of the latter group were males.

The analysis of the pathology of the thiouracil-treated glands resolves itself into two problems: (1) What is the specific effect, if any, of the drug on the histologic appearance of the gland? (2) What effect on the histologic evidences of activity or involution does thiouracil have? In order to analyze the two problems more clearly each will be considered separately.

SPECIFIC EFFECTS OF THIOURACIL

An attempt was made to determine if it was possible to say from the gross and microscopic examination that any individual specimen was from a patient treated with thiouracil. From the gross appearance there was nothing distinctive in the size, shape, or contour. The vascularity in some of the glands was accentuated, a feature which was particularly noted by the surgeon at the time of operation, but it was neither constant nor distinctive. This vascularity is similar to that noted in the primary hyperplastic glands removed prior to the time that preoperative iodine came into use.

The average weight of the primary hyperplastic glands from patients treated with thiouracil was 28 grams per lobe. For comparison, the average weight of 100 primary hyperplastic glands in cases in which iodine only was given was 24 grams per lobe. The 4 gram difference in the average weight is of doubtful importance and certainly is insignificant as far as any individual gland is concerned, since the lobe weight of the thiouracil

TABLE III.—DIAGNOSES (PATHOLOGIC) ON PRIMARY GLANDS

	Thiouracil per cent	No thiouracil per cent
Primary with early involution.....	19	6
Primary with moderate involution.	26	26
Primary with late involution.....	40	42
Primary with irregular involution..	15	28

group varied from 6 grams to 113 grams. Only one specimen was extraordinarily heavy. This was from a patient treated with both thiouracil and iodine and diagnosed as primary hyperplasia with early involution; the two lobes together weighed 225 grams. Those cases which were diagnosed as secondary hyperplasia were too variable to permit comparisons.

Microscopically, neither cells nor colloid appeared different in any respect from glands in the same stage of involution histologically when patients had not received thiouracil. In Table II is an analysis of the amount of lymphoid infiltration and stromal increase in the glands with the diagnosis of primary hyperplasia. Here again, there was no uniform increase or decrease and nothing greater or less than might be expected in a control group. The degree of lymphoid infiltration was somewhat greater in patients over 40 years of age. The length of time that the patient had received thiouracil or iodine made no apparent difference in the lymphoid or stromal response.

EFFECT OF THIOURACIL ON INVOLUTION

It would be reasonable to expect, from the results of the administration of thiouracil to animals, that thiouracil given to thyrotoxic patients might keep the gland in a state of histologic hyperplasia and that there would be little evidence of involution in many of the glands, even if iodine were given in addition. It has been noted (1, 3) that iodine added to the diet did not prevent the thiouracil effect on animals. Table III is a tabulation of the various pathologic diagnoses made on the primary hyperplastic glands when the patients had received thiouracil compared with a control group of 100 random primary hyperplastic glands of patients who had received only iodine. Although the thiouracil-treated cases tend to show a higher incidence of early involution—that is, there is considerable histologic evidence of activity—there are still numerous instances of later stages of involution.

TABLE IV.—DIAGNOSES ON PRIMARY GLANDS IN RELATION TO IODINE THERAPY

	Thiouracil only	Thiouracil and previous iodine	Thiouracil and preoperative iodine	Thiouracil and previous and preoperative iodine
Primary with early involution	1	1	4	3
Primary with moderate involution	1	2	7	2
Primary with late involution	2	2	9	6
Primary with irregular involution	1	3	0	3

Since few patients in whom the diagnosis was primary hyperplasia had not received iodine at some time or another, we must assume that the majority of the patients showed a picture which may have been influenced, in part at least, by the iodine. Table IV is a tabulation of the diagnoses made on the primary hyperplastic glands according to the time that the iodine was received in relation to the thiouracil treatment and the operation. Iodine did not constantly inhibit or further involution, no matter when it was used.

In order to determine more critically the response of the gland to thiouracil, an estimation of the histologic degree of activity of the thyroid was made in terms of basal metabolic rate points. While such estimations are only approximate, in the majority of cases with primary hyperplasia they are reasonably accurate. Cases of secondary hyperplasia were not considered in this manner because of the numerous irrelevant distorting features. The degree of activity thus estimated was compared with the basal metabolic rate at the beginning of thiouracil treatment. A definite

TABLE V.—HISTOLOGIC EVIDENCE OF INVOLUTION IN PRIMARY GLANDS

	Thiouracil only	Thiouracil and previous iodine	Thiouracil and preoperative iodine	Thiouracil and previous and preoperative iodine
No definite involution	2	4	8	6
Definite involution	3	4	8	5

involutionary response was considered, one in which the basal metabolic rate appeared to have dropped at least 20 points during the treatment. In Table V the responses noted are tabulated. The majority of the specimens showed involution. Only three glands showed an apparent increase in histologic activity during the treatment and two of these patients had had iodine. In 40 of the 47 cases the clinical response to thiouracil therapy was considered good as shown by a marked fall in the basal metabolic rate.

The degree of involution or lack of involution was not found to be dependent upon the manner in which iodine was given or upon age, sex, duration of symptoms, or duration of thiouracil treatment.

Glands classified as secondary hyperplasia, while more difficult to analyze in this manner, seemed to show similar involutionary changes.

COMMENT

Since relatively few of the patients of this series received only thiouracil as the preoperative medication, the comments and discussion must be limited chiefly to observations on the effect of thiouracil when it is used in conjunction with iodine.

The effects of thiouracil alone on glands from thyrotoxic patients are seemingly similar to the effects on glands of experimental animals, according to the reports of Moore and associates and Williams and Clute. Their specimens showed evidence of marked activity and with this the usual accompanying features of histologic activity such as increased size, vascularity and height of epithelium, loss of colloid, small acini, frequent lymphoid infiltration, and so forth. However, we do not believe that this "thiouracil effect" differs in any way from the picture seen in a hyperplastic gland in a comparable stage of activity in which no thiouracil has been used. There are no additional or pathognomonic features present in a thiouracil-treated gland which may not be present in a hyperplastic gland when thiouracil has not been given. In our opinion, it is not possible to examine a gland and to say from the gross or microscopic appearance of such a gland that the patient has had or has not had thiouracil treatment.

In the series of Williams and Clute (22 resected specimens) and of Moore and associates (26 resected specimens) there was apparently little evidence of involution except in one case of the latter series. In each group the patients were treated with thiouracil alone. These results contrast with the findings in our series in which the majority showed evidence of involution when treated with both thiouracil and iodine. Rawson, in comparing the appearance of biopsy specimens taken prior to thiouracil treatment to the histologic appearance of the gland in the surgical specimen removed later, concluded that in 4 of his 5 cases there was evidence of increased activity, while in 1 case about the same degree of activity was evident. It would appear that while thiouracil alone infrequently causes (or allows) definite histologic involution in a thyrotoxic patient, the addition of iodine to the treatment, either before or after the thiouracil is administered, may alter the microscopic picture considerably, with many cases showing good histologic involution.

It is difficult to place an interpretation on these results, largely because neither the cause of hyperthyroidism nor the mechanism of action of thiouracil or iodine is well understood. The addition of iodine to the thiouracil treatment did not cause involution routinely, nor as frequently as when iodine was used alone preoperatively. It was impossible to correlate the degree of histologic involution with such factors as age, sex, duration of symptoms, severity of symptoms, or length of time of either thiouracil or iodine therapy.

It has long been known that spontaneous remission of the symptoms of hyperthyroidism accompanied by morphologic evidence of involution in the thyroid gland may occur. Our material derived from thyroidectomies prior to the time when iodine came into general use as a method of preoperative medication, showed frequent evidence of spontaneous involution. A few patients after treatment with thiouracil alone have apparently been able to discontinue the drug without recurrence of thyrotoxic symptoms. Perhaps the involution found in some cases is a manifestation of a spontaneous remission and is independent of the thiouracil effect.

SUMMARY AND CONCLUSIONS

1. Thiouracil has been proved to be a most valuable drug for the preoperative preparation of patients with severe hyperthyroidism.

2. The drug must be administered until the maximum benefit is obtained and at that time subtotal thyroidectomy can be carried out without risk. The dose of thiouracil used was 0.6 gram a day, and it was found that approximately one day of treatment was required for each percentage of elevation in the basal metabolic rate. Previous administration of Lugol's solution prolonged treatment and those patients with hyperthyroidism of short duration responded more quickly.

3. The technical difficulties at operation which occurred in patients treated only with thiouracil have been overcome by the added use of Lugol's solution during the 3 week period immediately before operation; no thiouracil is given during the week immediately before operation.

4. Since thiouracil cannot be given without danger—evidence of toxicity occurred in 11 per cent of patients treated—patients must be carefully observed during treatment. Granulocytopenia is the greatest potential danger, so frequent blood tests are imperative.

5. Diagrammatic comparison is attempted of the altered pathologic physiology in the thyroid gland from normal during hyperthyroidism, under treatment with Lugol's solution, following thiouracil, and lastly, with combined administration of thiouracil and Lugol's solution.

6. The results of the study of 77 thyroid glands, surgically resected from patients with hyperthyroidism who had been treated preoperatively with thiouracil, are reported. Twelve of the patients were treated with thiouracil alone; the remainder had iodine in addition at some stage of the course of treatment.

7. From the gross and microscopic examination of an individual gland no specific effect was found which might be attributed to thiouracil. It was not possible to identify a thiouracil-treated specimen from a hyperplastic gland which has had no previous thiouracil therapy. However, some thiouracil-treated glands are larger than would be expected from the clinical course or microscopic picture.

8. The increased vascularity of the gland noted by the surgeon in those patients treated with thiouracil is of course not apparent in pathologic material.

9. When iodine is used in conjunction with thiouracil the majority of the specimens show histologic evidence of involution, especially when the microscopic picture is compared with the initial basal metabolic rate.

10. The addition of iodine to the treatment, either before or after thiouracil is administered, did not constantly bring about histologic involution; moreover, the incidence of involution was not as frequent as when iodine was used alone.

11. It was not possible to correlate the degree of histologic involution in this series with such factors as age, sex, duration or severity of symptoms, or duration of either thiouracil or iodine therapy.

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ESOPHAGOGASTROSTOMY IN THE TREATMENT OF CARDIOSPASM

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ESOPHAGOGASTROSTOMY is not intended as an initial procedure in the treatment of cardiospasm. The vast majority of patients who have cardiospasm obtain excellent results from dilatation of the cardia by means of the hydrostatic dilator, and it is only in the exceptional case that surgical intervention becomes necessary (10). It is not our purpose to review the general subject of cardiospasm, which has been very ably done in recent publications by Ochsner and DeBakey (11, 12), Gray and Skinner, and others. It would appear from a review of the literature of those cases of cardiospasm or achalasia of the esophagus in which surgical treatment was used that the best results were obtained in the group on which esophagogastrostomy was performed. Of the various surgical procedures employed, in general, those done through a transperitoneal approach have carried a much lower operative mortality rate than have the transpleural procedures.

As was pointed out by Lambert 30 years ago, and recently emphasized by Gray and Skinner, dilatation of the esophagus in cardiospasm usually assumes one of three typical forms: fusiform, flask-shaped, or sigmoid-shaped. In the fusiform type the lumen of the esophagus increases to a point midway between the cricoid cartilage and the cardia and then tends gradually to decrease in size; in the flask-shaped variety the dilatation is immediately above the cardia. In both of these types the cardia is the most dependent portion of the dilated esophagus and both can usually be relieved by hydrostatic dilatation. Cardiospasm in which the esophagus elongates as well as dilates, and therefore becomes sigmoid-shaped, is the rarest of the three types. Here, the increased length of the esophagus is accommodated by a curved course. The most dependent point of the dilated esophagus rests on the diaphragm to the right and posterior to the cardia; the esophagus then ascends to the left and enters the abdomen through the diaphragm at a higher level. A reservoir is thus formed below the level of the cardia. Gray and Skinner have pointed out that this angulation and this reservoir make dilatation from above more difficult and may militate against a satisfactory result.

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We have recently operated on 4 patients with cardiospasm of long standing in whose cases dilatation of the cardia had failed to produce more than temporary relief. The operative procedure employed in these 4 cases was esophagogastrostomy. Although in each case a very good functional result was obtained, the dilated esophagus did not appear to reduce appreciably in size following operation, an observation which has also been noted after esophageal dilatation.

CASE 1. A white farmer, aged 57 years, was referred to the Mayo Clinic on February 25, 1944, with the diagnosis of cardiospasm. At the time of his admission his esophagus had been completely obstructed for 6 days. His history dated back 10 years when, during the course of a respiratory infection, he first noticed difficulty in swallowing. This became gradually worse, leading to complete esophageal obstruction. Dilatation of the esophagus was carried out at home with temporary relief. During the 10 year interval there had been periods during which the patient had difficulty in swallowing but this was never prolonged and was not accompanied by complete obstruction. However, a second dilatation had become necessary 5 years before his admission to the clinic. When seen at the clinic during the latest episode, he stated that for 6 days he had been unable to swallow anything, liquid or solid. He was persevering in trying to eat but the food would seem to lodge in his esophagus. This produced retrosternal aching, palpitation, and slight dyspnea. Vomiting would occur soon after he ate. One liter of glucose solution had been administered intravenously 2 days before arrival.

The patient appeared chronically ill. He was markedly dehydrated and showed obvious loss of weight. His temperature was normal. His pulse rate was 100 and his blood pressure was 100 millimeters of mercury systolic and 80 diastolic. A loud systolic murmur was audible over the entire precordium. The edge of the liver was palpable one finger's breadth below the right costal margin. The prostate gland was moderately enlarged. Urinalysis revealed a specific gravity of 1.033 and occasional pus cells. The concentration of hemoglobin was 12.9 grams per 100 cubic centimeters of blood and leucocytes numbered 5,500 per cubic millimeter. Chemical examination of the blood disclosed no abnormality and a flocculation reaction for syphilis was normal. A roentgenogram of the thorax revealed widening of the mediastinal shadow due to dilatation of the esophagus secondary to cardiospasm. It also revealed pneumonia or re-expanding atelectasis of the upper lobe of the right lung (Fig. 1).

On the day of admission esophagoscopy was performed. About 1,500 cubic centimeters of foul smelling fluid was aspirated from the esophagus. After this, a bougie was passed

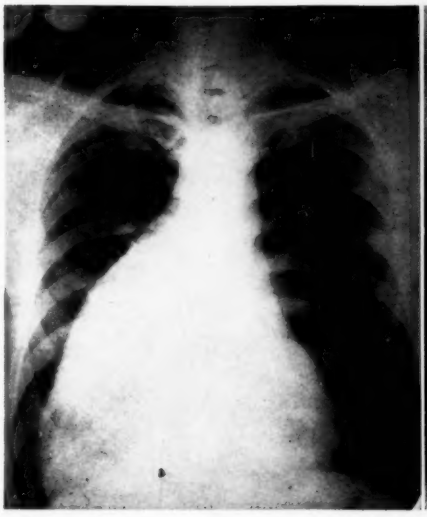

Fig. 1, left. Case 1. Posteroanterior view of thorax showing widening of mediastinal shadow due to dilated esophagus secondary to cardiospasm. Postoperative roentgenograms showed no significant change.

Fig. 2. Case 1. Anteroposterior view of esophagus showing marked dilatation and tortuosity. Flask-shaped variety which has become sigmoid.

into the stomach through the esophagoscope. A No. 21 F. sound with thread attached was then passed through the esophagoscope into the stomach and the thread was left in place while the esophagoscope was removed. Making use of the sound and attached thread as a guide, a No. 60 F. sound was passed for the purpose of dilatation.

After this procedure, the patient was somewhat relieved. However, it was necessary frequently to administer supplemental fluids intravenously, because he was unable to swallow an adequate amount. He continued to vomit periodically, sometimes immediately after meals and at other times several hours after meals. On some occasions the vomitus contained material just eaten and at other times it contained material eaten a day or two previously. Roentgenograms of the esophagus showed a characteristic sigmoid-shaped deformity secondary to cardiospasm (Figs. 2 and 3). During the next 30 days several dilatations with sounds and the Plummer hydrostatic dilator were performed. In spite of these dilatations, the patient obtained only temporary relief and continued to be unable to retain an adequate amount of food and fluid. His weight had fallen from 156 pounds (70.8 kgm.) to 120 pounds (54.4 kgm.) since the onset of his latest episode.

On April 10, 1944, the patient was operated on. Through a primary left upper rectus incision the abdomen was explored. Because of the patient's loss of weight, exposure was greatly facilitated. The esophageal hiatus admitted three fingers. The stomach was normal but the esophagus was tremendously dilated. The esophagogastric junction was quite constricted (Fig. 4). The remainder of the abdominal exploration revealed no abnormal findings. The upper end of the stomach and lower end of the esophagus were mobilized and esophagogastrostomy was performed by carrying out a procedure resembling a Finney type of pyloroplasty (Fig. 5). This consisted of a U shaped incision through the cardia and adjacent portion of the stomach and extending up into the esophagus. An outer row of interrupted silk sutures and an inner row of running chromic catgut sutures were used to approximate the adjacent margins of esophagus and stomach. The stoma provided by this procedure readily admitted three fingers. A few interrupted silk sutures were used to join the reflecting diaphragmatic peritoneum to the adjacent esophagus and

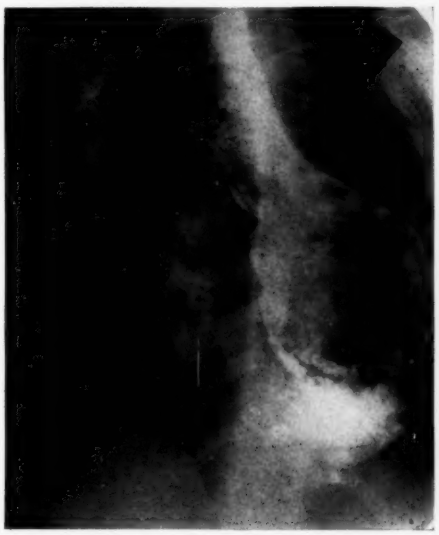

Fig. 3. Case 1. Lateral view of esophagus.

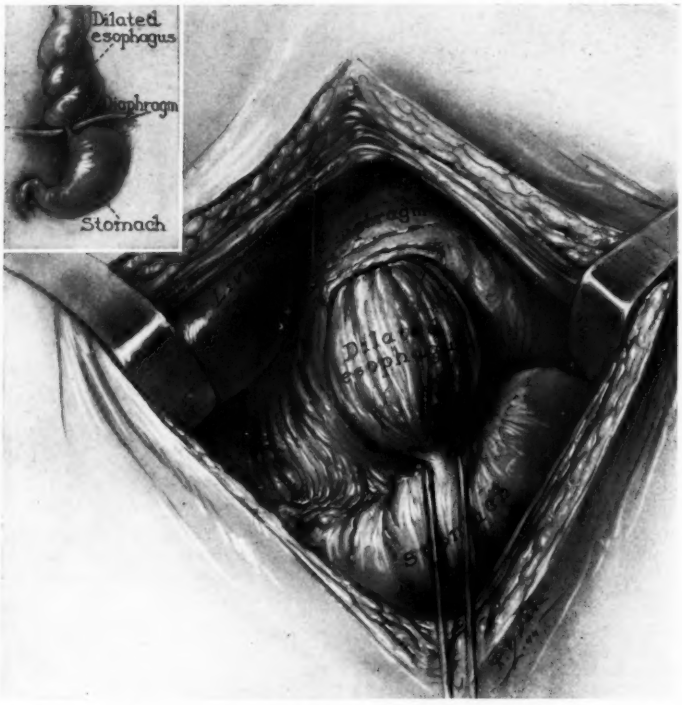

Fig. 4. Operative exposure. The left triangular ligament has been divided and the liver is retracted to the right.

stomach. Five grams of sulfanilamide were placed about the anastomosis and a Penrose drain was inserted down to this region. At first the patient experienced difficulty in swallowing adequate amounts of fluid or food but within 2 weeks he had discovered various foods which would pass satisfactorily. Twenty-five days after operation patient was permitted to return to his home. At this time the incision was healed and he was able to eat a liberal diet. A roentgenogram at this time showed no decrease in the size of the esophagus.

A letter received from patient September 27, 1944, stated that he weighed 151 pounds (68.5 kgm.) and that he was eating a liberal diet three times a day. However, he found it necessary to drink a generous amount of water with meals.

CASE 2. A white laborer, aged 44 years, registered at the Mayo Clinic on March 14, 1944. His chief complaint was dysphagia of 24 years' duration. The difficulty in swallowing had become progressively worse since its onset. At first he had noticed that on occasions solid food would seem to become lodged in his esophagus. He could force it down by drinking water. Later, even liquids became difficult to swallow. In 1922 dilatation of the esophagus was done at home and some relief was obtained. However, as the procedure was painful, he did not seek further dilatation. In 1942 a roentgenologic study was made. He was told that he had cardiospasm and a markedly dilated esophagus. Attempted dilatation was unsuccessful. He came to the clinic because he had been advised to have an operation, which he wished to avoid.

The patient appeared well nourished and not acutely ill. His general physical examination and laboratory studies gave essentially normal results. The roentgenologic diagnosis was cardiospasm with marked dilatation and tortuosity of the esophagus (Fig. 6).

Dilatation of the cardia by means of sounds and the Plummer hydrostatic dilator was carried out. The patient did not obtain adequate relief from the dilatations. He continued to have considerable difficulty in swallowing and it was thought advisable to consider surgical intervention.

On April 20, 1944, esophagogastrostomy was performed, a technique resembling the one described with reference to Case 1 being employed. A Rehfuss tube was passed through the nose beyond the anastomosis and into jejunum for temporary feeding. Exploration of abdomen revealed no abnormal findings other than marked constriction at esophagogastric junction and tremendous dilatation of esophagus.

On the day after operation water was administered continuously into the Rehfuss tube through a Murphy drip apparatus. This treatment was supplemented the following day with a high calorie jejunostomy formula. Then the patient was permitted to drink while the tube was still in place and on the 7th day the tube was removed. By this time the patient was taking a fairly adequate diet without distress. One week after the operation a wound infection became apparent. Hemolytic streptococci and micrococci were found in the culture. This infection was quite resistant to treatment, and the patient was not able to leave the hospital until the 24th postoperative day. He was able,

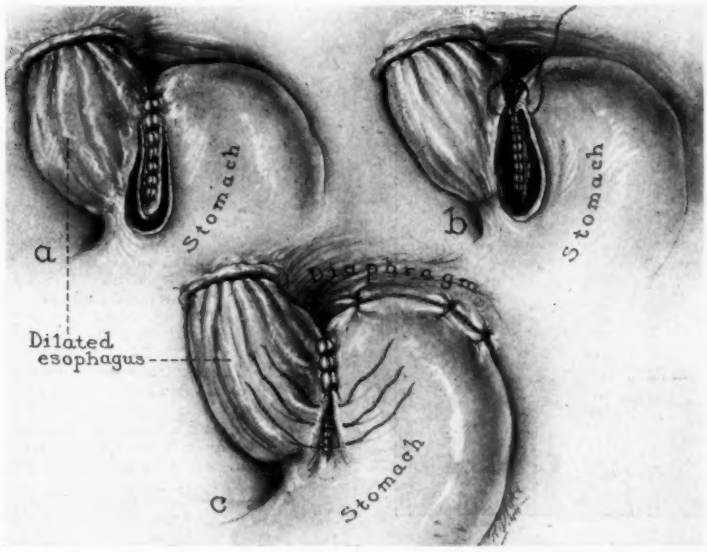

Fig. 5. Technique used in enlarging the stoma at the esophagogastric junction in cases 1 and 2. Note resemblance to Finney type of pyloroplasty.

however, to eat a liberal diet without distress. On May 31, 1944, he was permitted to return to his home.

September 26, 1944, patient visited clinic and reported he was getting along very well—had gained 24 pounds (10.9 kgm.) and was eating all types of food without distress.

CASE 3. A housewife, aged 53 years, was referred to the clinic on May 10, 1944, with a diagnosis of cardiospasm. She complained of dysphagia of 40 years' duration. At the onset, food would occasionally become lodged in her esophagus. She could force it down by hyperextending her neck or by increasing her intrathoracic pressure. Emotional stress seemed to aggravate this difficulty. She had vomited a great deal during her youth but in later years had vomited infrequently. On many occasions the vomitus contained food eaten a day or two previously. For several weeks prior to admission she had been having more difficulty than usual in swallowing both liquids and solid food. She had not lost weight. Subtotal abdominal hysterectomy had been done in 1939 for menorrhagia.

The patient was a moderately obese white woman. Her general examination and laboratory studies did not reveal any abnormal findings except for moderate hypertension. Her blood pressure reading was 150 millimeters of mercury systolic and 102 diastolic. There was an old, firm surgical scar in the lower midline of the abdomen. Roentgenoscopic examination of the thorax revealed an increase in breadth of the mediastinal shadow due to a dilated esophagus (Figs. 7 and 8). Roentgenoscopic examination and roentgenograms of the esophagus and stomach showed cardiospasm with marked dilatation of the esophagus.

On May 12, 1944, a No. 41 F. sound was passed over a previously swallowed silk thread. An obstruction was encountered 16 inches (41 cm.) from the incisor teeth. Esophagoscopy was then done and the esophagus angulated sharply to left of the midline 16 inches (41 cm.) below incisor teeth. In view of the angulation it seemed advisable to forego dilatation and proceed surgically.

On May 18, 1944, esophagogastrostomy was performed. Exposure was obtained through a left upper rectus incision. Exploration revealed a slightly enlarged but otherwise normal spleen. Subtotal hysterectomy had been done previously and the cervical stump was normal to palpation. The other abdominal viscera were normal except for tremendous dilatation of the distal portion of the esophagus and constriction of the cardia. The left lateral ligament of the liver and the peritoneal reflection from the diaphragm to the esophagus were divided. The esophageal hiatus was smaller than usual; hence, some of the crural fibers were divided to enlarge it. Two to three inches (5 to 8 cm.) of the esophagus were easily brought below the diaphragm. The junction of the esophagus with the stomach was greatly narrowed, measuring about 1.5 centimeters in diameter. This region was incised longitudinally through all layers and was closed transversely. An inner row of continuous chromic catgut suture and two rows of interrupted silk were used in the anastomosis. The stoma then measured at least 2.5 centimeters in diameter. Five grams of powdered sulfanilamide were scattered about the anastomosis, and a Penrose drain was inserted into this region.

On the day after operation atelectasis developed in the lower lobe of the left lung. The patient was able to cough up the mucous plugs, however, and the atelectasis cleared up spontaneously. On the 5th day sips of water were begun and by the time the patient left the hospital she was eating a liberal diet without distress. She was dismissed from the hospital 18 days after the operation and was permitted to return to her home 5 days later.

In a letter received from this patient on September 27, 1944, she stated that she was getting along very well. She had been eating a general diet three times a day. On three occasions she had had difficulty in swallowing but this was only momentary. She had also noticed a sensation of slight retrosternal pressure during the night on a few occasions. She had gained 9 pounds (4.1 kgm.) since return home.

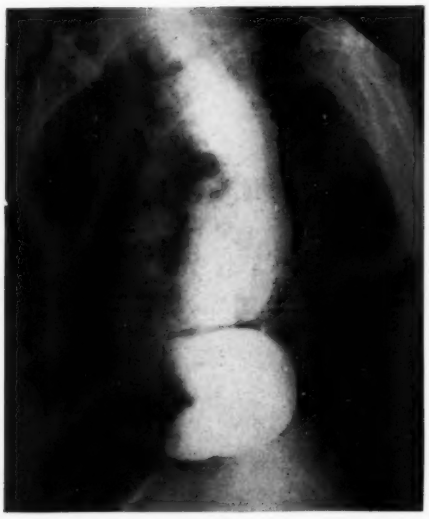

Fig. 6. Case 2. Lateral view of esophagus showing typical sigmoid deformity.

CASE 4. A 61 year old railroad yardmaster was first seen at the clinic on October 23, 1941. He complained of having had difficulty in swallowing solid food for 30 years. He usually had been able to wash the food down with large quantities of water. In the 6 months prior to admission he had also experienced difficulty in swallowing liquids. Whenever food became lodged in his esophagus, he experienced retrosternal aching. He had rarely vomited but obtained relief whenever he did. His cardia had been dilated 12 years prior to admission and again 7 months before he came to the clinic. Only temporary relief had been obtained on each occasion.

The patient was a well developed and well nourished middle aged white man. He had hypertension, his blood pressure being 190 millimeters of mercury systolic and 116 diastolic. There were left inguinal hernia and a moderate degree of prostatic hypertrophy. There were no other abnormal findings in his general physical examination. Urinalysis revealed occasional pus cells and erythrocytes. Blood counts and a flocculation test for syphilis gave normal results. The roentgenologic diagnosis was cardiospasm with marked dilatation of the esophagus (Figs. 9 and 10).

On October 27, 1941, the cardia was dilated until a No. 50 F. sound could be passed. On November 7, 11, and 17 dilatation by means of the Plummer hydrostatic dilator was carried out. An hour after the dilatation on November 17, 1941, the patient became acutely ill. His temperature rose to 104 degrees F. and he complained of severe epigastric pain. There was spasm of the anterior abdominal muscles. There was a question as to whether the patient had sustained a tear of the esophagus during dilatation of the cardia or whether aspiratory pneumonia had developed. He was quite ill for 3 weeks but responded to conservative management. He was able to return to his home on December 29, 1941.

This patient returned to the clinic on June 5, 1944. He stated that his difficulty in swallowing had persisted. Dilatation of the esophagus had been done elsewhere but there had been no appreciable relief from his distress.

The findings in his examination were essentially the same as when he was first seen at the clinic.

On June 12, 1944, esophagogastrostomy was performed. The abdomen was explored through a left upper rectus incision. Viscera other than the dilated esophagus and constricted cardia were normal. A longitudinal incision was made through the cardia and extended up into the esophagus and down into the stomach. The defect was closed transversely, with an inner row of continuous chromic catgut suture and an outer row of interrupted

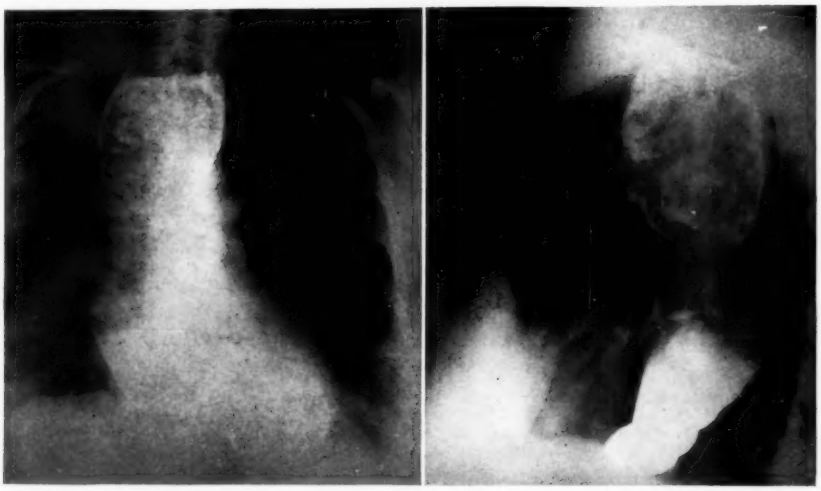

Fig. 7, left. Case 3. Anteroposterior view of esophagus.
Fig. 8. Case 3. Lateral view of esophagus showing fusiform variety which has become sigmoid-shaped.

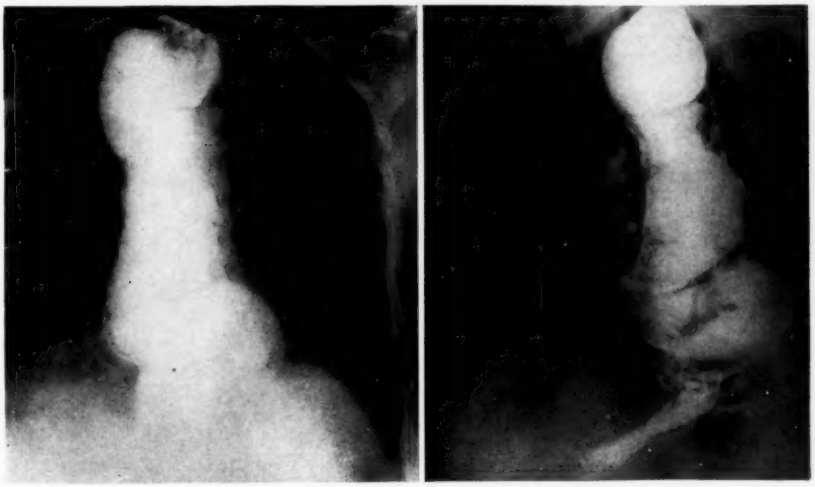

Fig. 9, left. Case 4. Anteroposterior view of esophagus showing typical sigmoid-shaped deformity of the dilated esophagus.

Fig. 10. Case 4. Lateral view of esophagus. Note marked tortuosity.

silk. The new stoma readily admitted two fingers. Five grams of powdered sulfanilamide was sprinkled about the anastomosis and two Penrose drains were inserted into this region. The postoperative course was uneventful. The patient left the hospital 10 days after the operation and returned to his home 6 days later.

A letter from this patient received September 11, 1944, stated that he had been eating all types of food without any difficulty whatsoever. He had gained 40 pounds (18.1 kgm.) since leaving Rochester and was working every day.

The great majority of patients suffering from cardiospasm can be treated successfully by hydrostatic dilatation of the esophagus. Approximately 70 per cent of these patients are completely relieved by one course of treatment. In 30 per cent of cases there is a tendency for the condition to recur. The recurrence may take place at any time from immediately after treatment to as much as 25 years after treatment. If the condition does recur, the great majority of patients can be successfully relieved by subsequent dilatation. Dilatation of the esophagus by means of the hydrostatic dilator can be employed with very little risk. In our experience the risk has been less than 0.1 per cent. In approximately 2 to 5 per cent of cases, hydrostatic dilatation does not prove efficacious and in these cases surgical intervention is indicated.

Of the surgical procedures which have been recommended, we prefer esophagogastrostomy performed through a transabdominal approach. A review of the literature and our own results indicate that this is a safe procedure, which accomplishes good results. Although good functional results are obtained, one should not expect retrogression in size of the dilated esophagus after the operation.

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CHONDROMALACIA OF THE PATELLA

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CHONDROMALACIA of the patella is a pathological entity and may be a cause of internal derangement of the knee. Buedinger first drew attention to fissure formation of the cartilage in the patella in 1906 and again in 1908 by reporting 15 cases in which operation had been performed. In 1910 Ludoff reported one case. Axhausen, in 1919, considered trauma to be the etiological factor and drew attention to the symptoms and physical signs in this condition. He advised excision of the impaired cartilage. Aleman is credited with first using the term, "chondromalacia of the patella," in 1916. Karlson followed Aleman's patients over a period of years and in 1940 reported 72 additional cases. The works of Aleman, Karlson, Silfvers iöld, Oberniedermayr, and Owre, are thorough and complete investigations of chondromalacia of the patella with follow-up examinations of the majority of cases in which operations had been carried out. Their conclusions as to the progress of the disease may be summarized as follows: 1st phase —patellar contusion, the cartilage being fissured; 2d phase—chondral malacia, the cartilage being raised and split by longitudinal and transverse fissures; 3d phase—degenerative chondral changes and synovitis.

Of 124 consecutive knee arthotomies performed at the 105th General Hospital, for internal derangement, there were 9 cases (7%) in which the cause of the derangement was found to be degeneration of the articular cartilage of the patella. This study is based upon these 9 cases and 2 similar ones in which operation was done by one of us (E. F. C.) in civilian practice. This relative frequency of occurrence suggests that the condition in the adolescent or the young adult is not uncommon and is frequently overlooked because: (1) while the history is suggestive of internal derangement of the knee, the physical examination is inconsistent, largely because of the difficulty in examining the articular surface of the patella; (2) the roentgenogram of the patella is negative; (3) at operation adequate exploration of the patella is frequently not carried out.

Chondromalacia of the patella may be the sole cause of symptoms, or it may be, in the later stages of development, associated with other pathological changes in the joint. The commonest associated changes are osteochondritis and injuries to the semilunar cartilages.

PATHOLOGICAL CHANGES

The typical appearance of well advanced chondromalacia of the patella resembles shredded crab meat. The articular surface of the patella presents a softened area with multiple striated fractures in the hyaline cartilage with particles of cartilage attached at the margin of the area (Fig. 1). In our cases the size of the area varied from three-eighths of an inch in diameter to essentially the entire surface of the patella. The location is most frequent in the center of the patella (Fig. 2), but at times the changes occur at the inferior margin or along the mesial border. The area of softening extends down to bone in the center, and toward the periphery of the area the changes are more superficial. Not uncommonly, small cartilaginous bodies are detached from the degenerated area and are found free in the knee joint. These become rounded and smooth. As time goes on these loose bodies may be partially or completely calcified (Fig. 1). In the early stages, changes in the joint may remain confined entirely to the patella, but after months or years, as abnormal friction between the patella and the femur develops, the secondary changes occur. These changes are thickening and congestion of the synovia, eburnation of the margins of the femoral and tibial condyles, and partial destruction of the articular cartilage, the last being most marked in the femoral condyles where they are in contact with the gliding patella.

Microscopic changes consist in a patchy proliferation of cartilage cells; the articular surface becomes quite cellular. The cartilage produced by these cells is irregular in surface contour, but does not differ in other respects from the normal. The same reaction is frequently seen about the periphery of cartilaginous loose bodies. The reaction is completely avascular and is not associated with infiltration of inflammatory cells (Figs. 3 and 4).

DIAGNOSIS

The diagnosis of chondromalacia of the patella should not be confused with injury to the semilunar cartilages although both conditions may ex-

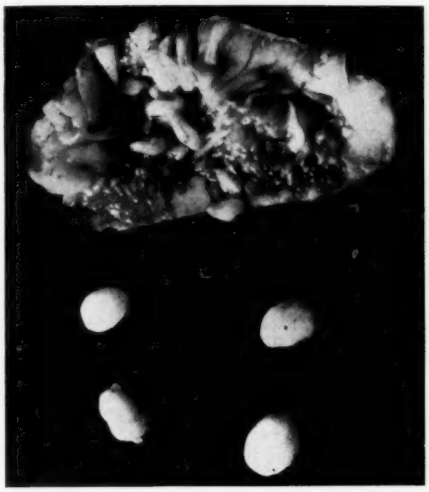

Fig. 1. An area of disintegrating cartilage excised from the articular surface of the patella, and four smooth rounded cartilaginous loose bodies which had become detached from the degenerated area and were removed from the knee joint at the time of operation. They contained no calcium and therefore were not demonstrable by roentgenogram. (Case 1.)

Fig. 2. Knee joint opened through a median parapatellar incision. Articular surface of patella turned upward demonstrating extensive area of chondromalacia in the central portion. There was thinning of the cartilage over the inner aspect of the medial femoral condyle. The synovia was markedly thickened and congested. Roentgenograms were entirely normal. (Case 5.)

ist in the same joint. One should exercise great care in palpating the articular surface of the patella by displacing it from side to side during the examination. Local tenderness under the patella may be the only positive finding, and even this may not be present if the pathological changes are confined to the center of the articular surface. It may be possible to produce pain by pressure or percussion over the patella with the knee acutely flexed.

Mechanism of injury. In our series of 11 cases symptoms were precipitated by an indirect twist of the knee in 5, a direct blow on the patella in 5, whereas in 1 there was no definite history of injury.

Symptoms. Pain was present either intermittently or continuously in all cases. Seven had recurrent swelling, 7 had infrequent catching or a sensation of weakness or "giving away" of the knee, and only 2 had a history of actual locking of the joint. In both of these cases loose bodies were found at operation.

Physical examination. On physical examination 7 patients presented increased synovial fluid, 6 had atrophy of the thigh, only 1 had fixed flexion deformity, 3 were slightly limited in flexion, and in 2 there was crepitus as the patella was moved over the femoral condyles. In only 4 was there definite tenderness over the mesial articular surface of the patella. It is probable that in some cases this very important sign was not looked for as diligently as it might have been. Tenderness along the mesial knee joint line was recorded in 6 cases. The reason for this finding is not clear. In 2 cases the patella was abnormally mobile laterally.

Therefore, given a patient with a history of intermittent pain over the anterior aspect of the knee associated with a momentary sensation of catching, followed perhaps by slight stiffness and moderate swelling of the joint, with atrophy of the thigh and tenderness along the mesial border and articular surface of the patella, one should strongly consider the diagnosis of chondromalacia of the patella.

X-ray findings. In all 11 cases roentgenograms of the patella were negative. In 3, however, there was evidence by roentgenograms of osseous loose bodies in the joint which presumably took origin from the inferior surface of the patella, and in 1 case there was moderate calcification of the tibial collateral ligament.

TREATMENT

The form of treatment to be employed is determined by the severity of the symptoms in the individual case.

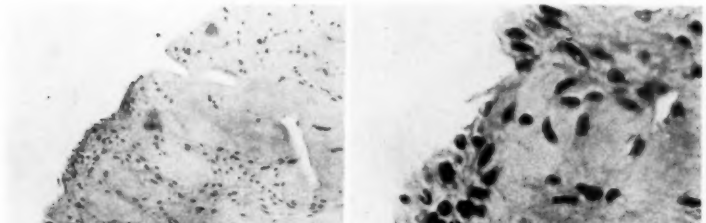

Fig. 3. Left, Low power: Section of cartilage from area of chondromalacia. Note the proliferation of cartilage cells, particularly at the surface, and the disruption of the usual architecture. (Case 1.)

Fig. 4. Right, High power: The same field showing the pycnotic hyperplastic cartilage cells. (Case 1.)

If the symptoms are mild and cause only an occasional disability from the knee, even though the diagnosis of chondromalacia of the patella may be reasonably certain, operation should not be carried out until the patient has been observed over a period of time, and then only if symptoms increase in severity. During this time exercises to maintain strength in the quadriceps muscles should be carried out.

In a patient with moderately severe symptoms with an occasional locking, or rather frequent catching in the knee which may be followed by pain, swelling and stiffness, operation is probably indicated. The knees should be explored through a parapatellar incision, and if the area of disintegrated cartilage is of moderate size, complete excision of the area should be carried down to bone. Loose cartilaginous bodies should be diligently searched for.

If an extensive area of chondromalacia is found covering essentially the entire surface of the patella, or if there is marked eburnation and thickening of the patella, the fourth or final stage of the process, one of two operative procedures is indicated: (a) A patellaplasty consisting in horizontal resection of approximately two-thirds of the patella with interposition between the bony surface of the patella and femoral condyle of a flap of fat and synovia turned upward from the infrapatellar region, or (b) complete removal of the patella. In all of our cases the changes in the patella found at operation were either moderately severe or extensive.

In 9 instances the degenerated area was removed by a sharp excision down to bone. In all of these there were cartilaginous bodies lying free in the joint which were also removed. In 3 of the 9 some of the loose bodies were calcified. In 1 patient the changes were so severe as to warrant patellaplasty. In 2 patients with associated recurrent lateral slipping of the patella, the tibial tubercle in each was transplanted mesially. In no case was the patella completely removed.

END-RESULTS IN 11 CASES

Six patients were returned to full military duty where they have remained for at least 1 year after operation. Three patients were returned to limited service duty following operation. One has remained at limited service duty for 17 months. The 2 remaining were returned to the United States because of chronic synovitis of the knee after periods of duty of from 12 to 15 months. The two civilians returned to school activities. One was completely relieved by operation; the other was definitely improved in that locking of the knee was eliminated, but occasional catching of the knee has persisted.

It is impossible to know the final disposition of all of these patients and the end-results of treatment cannot be determined until a period of years has elapsed. Therefore, all of them should be followed at yearly intervals to determine whether or not traumatic changes in the joint develop to a sufficient degree to interfere with the normal function.

SUMMARY

The purpose of this paper is to call attention to a condition which we believe has been frequently overlooked as a cause of internal derangement of the knee in adolescents and young adults. The patella should always be carefully palpated over the articular surface and when chondromalacia is suspected, and when symptoms justify operation, a parapatellar incision should be used in order to allow adequate exploration of the patella. If this condition remains unrecognized and untreated the knee will develop progressive changes resulting in what may be a severe degree of degenerative arthritis. The form of treatment should be determined by the severity of symptoms, and the extent of the changes in the patella found at the time of operation.

CASE SUMMARIES

CASE 1. A sergeant, aged 24 years, No. 2607, had pain and locking of the knee, of 16 months' duration, as the result of a twist of the knee. Examination revealed effusion, crepitus (marked), no atrophy, motions free, tenderness along medial joint line, patella stable. Roentgenogram was negative. The preoperative diagnosis was tear of the medial meniscus. At operation there were noted marked chrondromalacia of the entire surface of the patella; early thinning of cartilage over the lateral femoral condyle; 4 cartilaginous loose bodies (½ centimeter in diameter); and normal medial and lateral menisci. Treatment consisted of sharp excision of the articular surface of the patella, and removal of loose bodies. Patient was hospitalized 47 days. He was returned to full military duty, where he has remained for 15 months as an electrician, requiring extensive climbing.

CASE 2. A private, aged 22 years, No. 892, had pain, and stiffness and weakness of knee, which had persisted for 8 years. There was no locking. The symptoms were the result of a direct blow on the patella as a result of a fall. Examination revealed effusion, ¾ inch atrophy of thigh, stable patella, tenderness over lateral joint line and femoral condyle. Knee motions were normal. Roentgenogram revealed 1 loose body ¾ inch in diameter. The preoperative diagnosis was loose body. At operation, the following were found: extensive (s vere) cartilaginous degeneration of the entire articular surface of the patella, one large loose body, 1.5 centimeters in diameter. Treatment consisted of sharp excision of the disintegrated cartilage of the patella and removal of the loose body. Patient was hospitalized 25 days. He was returned to full military duty, where he has remained for 22 months as ground crewman in Air Corps.

CASE 3. A private, aged 40 years, No. 10822, had had recurrent pain in the knee, over a period of 20 years. There was no locking. The cause was not known. Examination revealed effusion, tenderness over the medial joint line, but no atrophy. Extent of motion was 5 degrees' fixed flexion, 15 degrees in limited flexion. Roentgenogram was negative. The preoperative diagnosis was tear of the medial meniscus. At operation the findings were moderately severe chondromalacia of the central area of the patella. The menisci were normal. Treatment consisted of excision of the disintegrated cartilage of the patella. Patient was hospitalized 63 days. He was returned to full military duty. Patient remained at full duty for 1 month and was then returned to the United States by another hospital. The patient had no medical record for basis of disposition.

CASE 4. A private, aged 21 years, No. 10806, had had recurrent pain, "giving away," and swelling of the knee of 3 years' duration. There was no locking. The condition was the result of a direct blow to the outer side of the knee. Examination revealed no effusion, a ¾ inch atrophy of the thigh, tenderness along the medial border of the patella, stable patella. There was complete range of motion of knee. Roentgenogram was negative. The preoperative diagnosis was chondromalacia of the patella. At operation, the findings were moderately severe chondromalacia of the center of the patella (2 cm. in diameter). Treatment consisted of sharp excision of the area. Patient was hospitalized 70 days. He was returned to full military duty, where he has remained for 9 months as an infantryman.

CASE 5. A sergeant, aged 24 years, No. 7574, complained of recurrent pain, swelling, and "catching" of the knee, of 4 years' duration, as the result of a football injury. Examination revealed no effusion, no atrophy, tenderness over the medial joint line and the medial femoral condyle. Motions of knee were complete. Roentgenogram revealed a "loose body." The preoperative diagnosis was chondromalacia of patella. The operative findings were severe chondromalacia of two-thirds of the articular surface of the patella most marked in the central area; early degenerative changes of the medial femoral condyle; loose body 1 centimeter in diameter. Treatment consisted of removal of the disintegrated cartilage by sharp dissection down to the bone. The patella surface was covered by a flap of synovia turned up from the infrapatella area. Patient was hospitalized 90 days. He was returned to full military duty, where he has remained for 11 months as an instructor in reconditioning cadre.

CASE 6. A private, aged 24 years, No. 3339 had had intermittent pain and swelling of the knee for 3 months. There was no locking. The condition followed a twist of the knee. Examination revealed no effusion, 1 inch atrophy of thigh, motions of knee complete; marked crepitation on motion of patella. Roentgenogram revealed partial calcification of the tibial collateral ligament. The preoperative diagnosis was osteochondritis of the femoral condyle. At operation the following were noted: moderately severe chondromalacia of patella most marked in central area (2 cm. by 3 cm.). Two cartilaginous loose bodies lying free in the joint. Treatment consisted of sharp excision of the degenerated cartilage down to the bone. Patient was hospitalized 52 days. He was returned to limited service duty, where he has successfully completed 17 months of guard duty.

CASE 7. A private, aged 24 years, No. 12028, complained of intermittent pain, swelling, "giving away" of the knee, of 15 months' duration. The condition followed a direct blow on the patella. Examination revealed ½ inch atrophy of thigh, no joint effusion, tenderness along medial border of patella and joint line. There was pain on lateral displacement of the patella. Roentgenogram was negative. The preoperative diagnosis was chondromalacia of the patella. At operation the findings were marked chondromalacia of the central and inferior area of the articular surface of the patella; 3 cartilaginous loose bodies free in the joint (melon seed size). Treatment consisted of sharp excision of the degenerated area of the cartilage and removal of the loose bodies. Patient was hospitalized 90 days. He was returned to limited service duty. Patient performed this limited service duty for 1 year after which he was readmitted to this hospital and returned to the United States because of chronic synovitis of the knee.

CASE 8. A corporal, aged 29 years, No. 1440, complained of pain, swelling and weakness of the knee, of 16 years' duration. There was no locking. Condition was the result of a direct blow on the patella. Examination revealed

marked tenderness along the mesial border of the patella, the patella being abnormally mobile laterally. Roentgenogram was negative. The preoperative diagnosis was recurrent dislocation of patella; chondromalacia of the patella. The operative findings were: severe chondromalacia of patella, 2½ centimeters in diameter, most marked in the central and inferior articular surface of the patella; several cartilaginous loose bodies free in the joint. Treatment consisted of patellaplasty with interposition of a flap of fat and synovia between the patella and femoral condyles, and transplantation of the tibial tubercle mesially. Patient was hospitalized 25 days. He was transferred to another general hospital where he was sent to limited service duty. He was readmitted to a general hospital after 15 months' duty and returned to the United States with diagnosis of synovitis of the knee.

CASE 9. A private first class, aged 26 years, No. 13376, complained of pain and swelling of the knee of 5 weeks' duration. There was no locking. Condition was the result of a twist of the knee. Examination revealed effusion, tenderness along the medial border of the patella, no atrophy of the quadriceps. Roentgenogram revealed one loose body. The preoperative diagnosis was loose body; chondromalacia of patella. The findings at operation were moderately severe chondromalacia of the central and mesial articular surface of the patella, 2 centimeters in diameter; one cartilaginous loose body attached to the articular cartilage of the patella; two loose bodies in the lateral aspect of the joint, one of which was calcified; mild osteochondritis of the lateral femoral condyle. Treatment consisted of sharp excision of the disintegrated articular cartilage of the patella down to the bone. Patient was hospitalized 75 days. He was returned to full military duty, where he has completed 3 months of guard duty.

CASE 10. A civilian, aged 15 years, U. S. A., complained of frequent catching, "giving away," and pain over both sides of the knee associated with slight swelling of the knee of 6 months' duration. Condition was the result of a twist of knee while skating. Examination revealed moderate effusion, ¼ inch atrophy of the quadriceps, tenderness along the medial tibiofemoral fossa, 20 degrees of fixed flexion. Roentgenogram was negative. The preoperative diagnosis was injury of the medial meniscus. The operative findings were: smooth crater defect 1 centimeter in diameter in the articular cartilage of the patella; one cartilaginous loose body in the quadriceps pouch which corresponded in size to the defect in the patella; moderate increase of joint fluid, which contained small flecks of detached cartilage. Treatment consisted of removal of the loose body. Patient was hospitalized 21 days. He was returned to school, complained of persistent "catching" of the knee, but knee did not lock.

CASE 11. A civilian, aged 16 years, U. S. A., complained of frequent "catching" of the knee accompanied by a "wham." There was no swelling. Symptoms had been present 1 year. Condition was the result of a direct blow to the patella while playing football. Examination revealed a normal knee except for marked atrophy of the quadriceps group. Roentgenogram was negative. The preoperative diagnosis was osteochondritis. The findings at operation were marked cartilage destruction of the central portion of the patella; 2 small loose bodies 4 millimeters by 6 millimeters. Treatment consisted of excision of the area of chondromalacia down to the bone, drilled. Patient was hospitalized 21 days. He was returned to full school activities. Patient's knee was symptom free when seen 9 months after operation.

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CHANGES IN CHRONAXIE DURING DEGENERATION AND REGENERATION OF EXPERIMENTALLY PRODUCED LESIONS OF THE SCIATIC NERVE OF THE CAT

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TO be an effective stimulus for nerve or muscle, an electrical current must be of a certain liminal strength and must flow for a certain liminal duration of time. As the duration of the stimulus is shortened, so must the strength of the current be increased. When one plots the strength of the current necessary to produce contraction of a muscle against the durations of the current, a strength duration curve is obtained. In general, it is difficult to compare the whole of such a curve obtained at one time of degeneration or regeneration with the whole curve obtained at another time. It is also difficult to compare a whole strength duration curve obtained from the examination of one person to that of another. In part, this is due to the fact that the curve bears a certain relationship to the rheobase, or the minimal current which will stimulate muscle or nerve at long durations, usually over a second and frequently designated as of "infinite duration." For this as well as other reasons concerned with the kinetics of stimulus, it has been found more desirable to compare some point on a curve to a similar point on another curve. Such a point is that time constant designated as chronaxie. This is the current duration at which the strength of the current necessary to produce contraction of muscle by a current of infinite duration (rheobase) is doubled.

Since the early work upon this time constant, or chronaxie, by Lapicque and Lucas, many investigators have contributed to its study. For the most part, the studies have been conducted by physiologists. Just as it had been found that muscles which contract and relax slowly have a longer chronaxie and those which contract rapidly have a shorter chronaxie, so was it found that when a muscle was denervated, and its contraction and relaxation slow, its chronaxie increased markedly. Although the chronaxie of different muscles of man each have a somewhat different chronaxie, the average chronaxie of the normal muscle is a fraction of a millisecond, usually less than 0.5 milliseconds; that for the flexor sublimis digitorum, for example, being 0.00021 second. When the muscle is denervated, the chronaxie may be increased over 100 times or more.

The reason for this is stated by Watts as follows: "The great increase in the 'chronaxie' observed in human subjects after denervation is due not to any alteration in the time constants of the muscle fibers, but merely to the point of incidence of the stimulus shifting from nerve to muscle." Since the time constant for nerve is short (0.0005 second or less) and that for muscle is long (0.008 second or more), the chronaxie of the denervated muscle in which no nerve is present will be found to be quite long. This marked contrast between the short chronaxie of the normal muscle and the long chronaxie of the denervated muscle has led to the use of determination of chronaxie as a procedure for the diagnosis of the severity of a lesion of nerve and prognosis as to its recovery.

Many have reported upon the use of chronaxie determinations in man for diagnosis and prognosis. Among them may be mentioned Bourguinon.

Modifications based upon the same principles of kinetics of stimulus have likewise been used very widely during World War I; such modification was the Lewis Jones method of using a constant strength of voltage to determine the minimal duration at which contraction of muscle occurred.

The use of these methods has not found much favor among American neurologists and neurosurgeons. This is partly due to the fact that different types of apparatus gave different results; that in many cases apparatus was faultily designed; that accurate measurements of current and time could not be made by methods employing condenser discharges; and largely because of the tedious character of the examination and time necessary.

In the literature dealing with the use of chronaxie as a diagnostic and prognostic procedure in

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The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University.

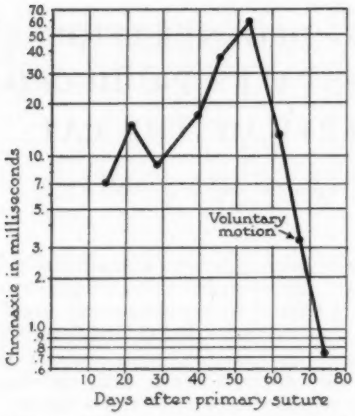

Fig. 1. The evolution of changes in chronaxie of the gastrocnemius muscle at various days following primary suture of the sciatic nerve.

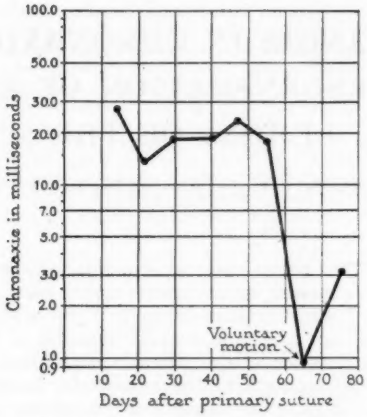

Fig. 2. The evolution of changes in chronaxie of the gastrocnemius muscle at various days following primary suture of the sciatic nerve.

man, it is difficult to find reports of measurements performed at regular intervals after injury or suture throughout the periods of degeneration, denervation, and regeneration. Rather, there is found one measurement, sometimes more, of many different cases at different stages of change in muscle. For that reason we do not have a clear understanding of the evolution of changes in chronaxie after denervation and during regeneration. That the enormous lengthening of the chronaxie is a clear indication of denervation cannot be questioned. A number of other questions require an answer. First, what are the changes that indicate recovery? Second, do they antedate recovery of motion or sensation? Third, does the determination of chronaxie give as early and as accurate indications of recovery as other methods?

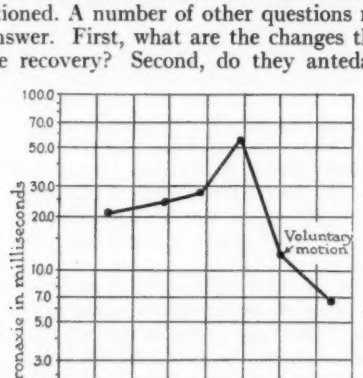

Fig. 3. The evolution of changes in chronaxie of the gastrocnemous muscle at various days following primary suture of the sciatic nerve.

To answer these questions we sectioned and immediately sutured the sciatic nerve of 5 cats; at regular and frequent intervals the muscles supplied by the injured and later regenerating nerve were stimulated by square wave currents of varying durations and strength duration curves plotted. A study of the evolution of the changes in chronaxie was made possible and these changes were compared to strength duration curves obtained from the examination of denervated and recovering muscle in man. As a result of this study certain conclusions will be made.

METHOD

The method for obtaining an impulse of rectangular wave shape lasting for as little as 30 microseconds has been described by us before (5). The duration of the impulse was controlled by two gas filled triodes, one of which served to initiate the flow of current while the second served to stop it. A constant flow of current through the tissue was maintained by a pentode operated on the saturated portion of its characteristic. Thirty-three different time intervals, selected to conform to a logarithmic scale, were made available. The indifferent electrode placed over the heel measured 1.5 centimeters; the exploring one, 4 millimeters, was placed over the belly of the muscle. The rheobase was determined by finding the threshold value of current when the impulse lasted 1 second. Then threshold values of current were found for successively shorter durations of the

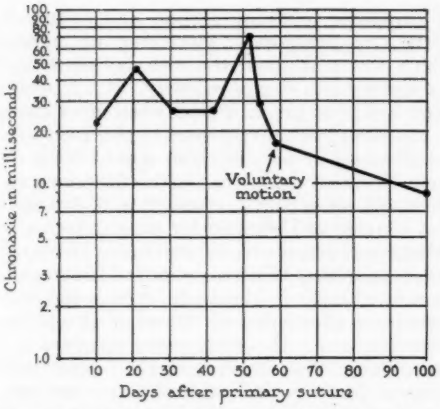

Fig. 4. The evolution of changes in chronaxie of the gastrocnemius muscle at various days following primary suture of the sciatic nerve.

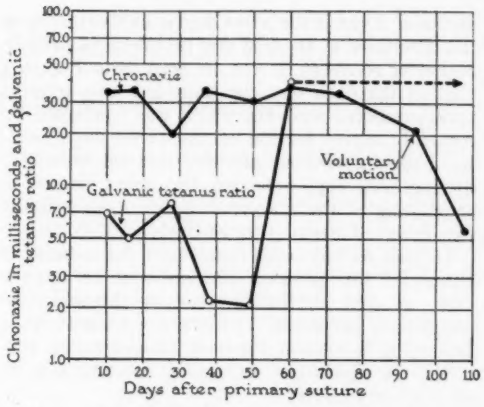

Fig. 5. Graphs of changes in chronaxie and tetanus ratio of the gastrocnemius muscle at varying days after primary suture of the sciatic nerve, in a cat in which regeneration was delayed by neuroma formation.

impulse. It was possible to use as much time as was necessary to observe the amperage in a suitable milliammeter by shunting the specimen out of the circuit, thereby avoiding painful unbearable stimuli and severe polarization changes.

RESULTS

Our first examination was made usually from the 6th to the 14th day after the primary suture. Then examinations were made from 5 to 7 days apart until motor function had well recovered. In all of the gastrocnemius muscles of the 5 cats, at the 9th, 10th, 13th, 14th, and 15th day, the chronaxie had lengthened from a fraction of a millisecond to 21, 34, 21, 27, and 7 milliseconds (Figs. 1, 2, 3, and 4). In 4 of the 5 animals the chronaxie continued to lengthen somewhat, from 21 milliseconds at the 9th day to 47 milliseconds at the 21st day; from 34 milliseconds at the 10th day to 35 milliseconds at the 19th day; from 21 milliseconds at the 13th day to 24 milliseconds at the 27th day; and from 7 milliseconds at the 14th day to 15 milliseconds at the 21st day.

Then in 4 of the 5 animals there was a shortening of the chronaxie from 47 milliseconds at the 21st day to 26 milliseconds at the 31st day; from 35 milliseconds at the 19th day to 20 milliseconds at the 27th day; from 27 milliseconds at the 14th day to 13 milliseconds at the 21st day; and from 15 milliseconds at the 21st day to 8.8 milliseconds at the 27th day.

This shortening in chronaxie at times to one-half of that present before is, of course, not an indication of recovery. That a shortening of chronaxie occurs at this time during the state of degeneration of the muscle should be emphasized and remembered. The shortening of chronaxie occurs about the same time as we have found a temporary rise in the rheobase, in threshold and ratio for progressive current stimuli and threshold and ratio for galvanic tetanus to occur. The cause for these changes is as yet unknown (Fig. 5).

Following this there is a progressive lengthening of chronaxie to a peak which was reached at the 49th, 49th, 53rd, 53rd, and 60th days with a chronaxie of 56 milliseconds, 23 milliseconds, 60 milliseconds, 72 milliseconds, and 38 milliseconds, respectively.

Once the peak of the lengthened chronaxie had been reached and, as the result of regeneration, began and continued to shorten, the shortening process was rapid and of a considerable order. The answer to the question as to whether such a rapid and significant shortening of chronaxie occurred before signs of recovery of motion had occurred or earlier than signs detected by other methods of electrical examination, was made possible by delayed recovery in one of the cats. The delay was found to be due a large neuroma, when the operative site was explored because motor function had not occurred at the expected time.

In this case, the chronaxie had lengthened to 34 milliseconds on the 10th day after primary suture. On the 17th day it was 35 milliseconds and then it shortened to 20 milliseconds on the 27th day. On the 37th day it had again lengthened to 35 milliseconds and continued between 31 and 37 milliseconds to the 72d day. On the 93d day it shortened to 20 milliseconds and on the 108th day only, was there a sharp shortening to 5.6 milli-

seconds. Even if the lesser degree of shortening of the chronaxie at the 93d day be taken as an indication of recovery, it can be seen from Figure 5 that at the 60th day the large galvanic tetanus ratio predicted recovery which was confirmed by return of active motion on the 108th day. Thus, the large increase of galvanic tetanus ratio predicting recovery, preceded the lesser degree of shortening of the chronaxie by 33 days and the significant shortening by 48 days (Fig. 5).

In man we have also found that the increase of threshold for galvanic tetanus and of tetanus ratio as well as the increase of threshold for progressive current and progressive current ratio, indicating successful regeneration of a nerve, preceded the significant shortening of chronaxie indicative of recovery.

We have already called attention to the fact that discontinuities in the strength duration curves which are indicative of regeneration of a nerve may be seen during the time that chronaxie may continue to lengthen and seem to give indication of continuation of the degeneration of the muscle. In a group of spontaneously recovering peripheral nerve injuries in man, the number of instances in which the chronaxie had significantly shortened (15 milliseconds or less) was about the same as those in which the galvanic tetanus ratio was high. However, at times the galvanic tetanus ratio was low and the chronaxie short. At other times, the chronaxie was long and the galvanic tetanus ratio high. When evidence of some denervated muscle was obtained by a low galvanic tetanus ratio and in the same muscle evidence of some neurotized muscle was shown by a short chronaxie, the combination gave excellent indication of a spontaneously recovering nerve.

When however, a nerve had been operated upon a considerable time before electrical examination was made, whether motion or sensation had recovered or not, the number of instances of high galvanic tetanus ratio exceeded those in which chronaxie had shortened. Nevertheless, in some a low galvanic tetanus ratio and a short chronaxie indicated recovery.

It is obvious, therefore, that it is of value to measure the chronaxie as well as the galvanic tetanus ratio.

SUMMARY

The marked lengthening of chronaxie from that of a fraction of a millisecond in normal muscle to one of 100 or more times is indicative of a denervated muscle. After the initial marked lengthening of chronaxie following section and suture of a nerve, the temporary shortening of chronaxie which occurs at about the 26th day must not be interpreted as a sign of recovery. It is a phenomenon which occurs at a time when other changes in characteristics of responses to electrical stimuli usually seen at recovery also appear for a short time. These are the increase in rheobase, increase in threshold for galvanic tetanus and of tetanus ratio, increase of threshold for progressive current stimuli and progressive current ratio. The cause of this is unknown. When one then follows the evolution of changes in chronaxie, it is found that a significant shortening of chronaxie is associated with recovery. However, when recovery is delayed this occurs much later than other indications of recovery derived from other methods of electrodiagnosis. Even when not delayed, when regeneration of a nerve is progressing, other signs precede shortening of chronaxie as an indication of recovery. However, the combination of a low galvanic tetanus ratio with a short chronaxie is characteristic of spontaneously recovering lesions and at times of recovery after operations upon injured nerves.

CONCLUSIONS

1. The marked lengthening of chronaxie from that of a fraction of a millisecond to that 100 or more times longer is a clear indication of denervated muscle.

2. The temporary shortening of chronaxie during the course of degeneration of muscle is not a sign of recovery.

3. Significantly great shortening of chronaxie from its final peak of great length is a sign of recovery.

4. This sign of recovery occurs later than signs derived from other electrical examinations, such as tetanus ratio, and may not occur until motor recovery is present.

5. The combination of a low galvanic tetanus ratio with a short chronaxie is characteristic of spontaneously recovering lesions and at times of recovery after operations upon injured nerves.

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EXPERIMENTAL CHOLECYSTITIS

Final Results of Vaccine and Filtrate Therapy

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IN a tabular review of the literature on cholecystitis (2) the bacterial studies on 2162 diseased gall bladders removed at operation seemed to indicate that the organisms most frequently present were streptococci similar to those infecting the nose, throat, teeth, and bowel; the Staphylococcus aureus, as in sinus disease; and members of the typhoid colon group. Our experiments, conducted over a 15 year period, were carried out with over one hundred antigens obtained from patients in the Jefferson Hospital. In the first series, in which 16 strains of 7 different types of organisms were injected into 88 rabbits, some degree of chronic cholecystitis was produced with organisms from each group, the most effective being a nonhemolytic streptococcus isolated from the bowel of a patient suffering from chronic cholecystitis and colitis. Inoculation of 66 of the 88 rabbits with the nonhemolytic streptococcus caused gall-bladder disease in 13 (20 per cent). In a later communication (1) on the use of various bacterial organisms it is reported that 44 strains of 7 different types of organisms were used in 129 rabbits, resulting in 25 diseased gall bladders (approximately 20 per cent).

Ascending doses were injected intravenously into the rabbits' ears, usually beginning with 0.02 cubic centimeter of 6 hour culture, and repeated in larger doses once or twice a week, dependent upon signs of morbidity in the animal. Frequently injections were discontinued after the third or fourth small dose, but in other cases the dose amounted to 3 cubic centimeters of a 24 hour culture. Realizing that in some cases we had used too large amounts of the antigen, which tended to produce acute rather than chronic cholecystitis, we decided to modify the technique.

While aware of the virtual impossibility of duplicating in the experimental animal focal infection as it may exist in man, nevertheless we hoped to simulate this condition as closely as possible. Therefore, small intravenous injections of 0.02 to 0.05 cubic centimeter of an 18 to 24 hour culture were repeated twice a week unless contraindicated by the condition of the rabbit (1). One hundred sixty-six animals were injected with the viable strain of Streptococcus nonhemolyticus (antigen 7) until, presumably, chronic illness was clinically evident. Eighty-four diseased gall bladders (51 per cent) were obtained.

The animals were then segregated into groups of 3 individuals: control, vaccine-treated, and filtrate-treated, the selections being based on similarity of response to the culture inoculation—the temperature and weight changes and presence of joint disease. (With the nonhemolytic streptococcus we have observed a high incidence of joint disease associated with gall-bladder lesions.) When it was impossible to select 3 animals with similar manifestations, those in the poorest condition were placed in the control group. On this basis 59 were retained as controls, 50 were inoculated with vaccine, and 57 were treated with filtrate.

These series were further subdivided according to the nature of the dietary regimen (adequate in some cases and inadequate in others), and the results obtained led us to believe that the animals on an inadequate diet responded less favorably to treatment than did those which were adequately fed. Furthermore, the treatment with autogenous vaccine apparently yielded more satisfactory results than did treatment with the filtrate.

Since then we have employed the same method of experimentation on a further series of 224 animals, with this exception: After completion of the infective phase the animals were arbitrarily selected for grouping as follows—*triad 1*, the rabbit apparently in the best physical condition was placed among the controls, and that in the poorest among the vaccine treated; *triad 2*, the poorest animal was placed among the controls, and the best in the vaccine treated; *triad 3*, the healthiest animal was selected for the filtrate treated group, the poorest for the controls. Employing this procedure for each selection of 3, the best and poorest animals were evenly distributed throughout the 3 groups. In this way we felt we had avoided prejudice in the selection of animals for treatment.

We shall present here a detailed interpretation of the data obtained by gross studies at necropsy on the 224 animals (74 control, 75 vaccine treated, and 75 filtrate treated) that lived, maintained on an adequate diet, throughout the planned term of

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TABLE I.—GROSS PATHOLOGY ASSOCIATED WITH GALL-BLADDER DISEASE

SERIES OF 224 ANIMALS, ANTIGEN 7

	Number of lesions	Percentage of lesions
Gall-bladder lesions, gross total	153	68.3
Gall-bladder diseased, bile normal	86	38.4
Gall-bladder diseased, bile abnormal	67	29.9
Gall-bladder diseased, no coexistent disease	18	8.0
Gall-bladder diseased, with concurrent kidney lesions	21	9.4
Gall-bladder diseased, with concurrent joint lesions	55	24.6
Gall-bladder diseased, with coexistent organic and joint lesions	59	26.3

treatment. The 11 control, 6 vaccine treated, and 14 filtrate treated rabbits which either died or were killed, to prevent postmortem changes, when death seemed imminent, are not included in this report because autopsy disclosed that they suffered for the most part from an acute bacterial infection. The fact that so few animals died after initiation of the treatment phase of the experiment is perhaps indicative of our success in selecting the chronic cases on the basis of clinical evidence.

Microscopic studies on this series will be reported later. Nine normal animals selected from the same stock showed no evidence of gross or microscopic change at necropsy.

Table I summarizes the gross pathologic findings on the gall bladder, observed at necropsy on the 224 animals. It is to be noted that approximately one-third of those with cholecystic disease showed coexistent kidney and joint infection. Elsewhere we shall present the studies on associated lesions.

Table II gives general findings on bacteriological study of cultures recovered during necropsy.

Only 37, or 16.5 per cent, of the animals had an active infection, and in only 20, or 8.9 per cent, was the viable Streptococcus nonhemolyticus present in the bile. At first glance it may be thought that the recovery of the organism from the joints closely parallels that from the bile. However, it must be borne in mind that only 13 rabbits, 5.8 per cent, disclosed some active infection of the joints on necropsy. The remaining 3 joint cultures were from rabbits having multiple joint infection. It is apparent, therefore, that in both gall-bladder lesions and coexistent joint and kidney lesions the organs were frequently sterile.

FURTHER DATA ON CULTURE INJECTIONS—VIABLE ORGANISMS—224 ANIMALS

In the control group with adequate diet there were 74 animals. The total number of injections

TABLE II.—POSITIVE CULTURE RECOVERY

	Number	Percentage
Animals with 1 or more cultures	37	16.5
Total positive cultures	55	24.5
Bile, cultures from	20	8.9
Joints, cultures from	16	7.1
Kidney or urine, cultures from	10	4.5
Other sources, cultures from	9	4.0

given was 1301, the average injections numbering 18. The period of injections covered a minimum of 3 days to a maximum of 8 months. The range of injections was 1 to 58.

In the vaccine treated group with adequate diet, there were 75 animals, with an average number of injections of 18. The total number of injections was 1357. The time range of injections in the series varied from 3 days to 7¾ months. The range of number of injections was 1 to 52.

In the filtrate treated group with adequate diet, there were 75 animals with an average number of injections of 19. The total number of injections was 1320. The time range of injections (when more than 1 was given) varied from 3 days to 9¼ months. The range of number of injections was 1 to 60.

DURATION OF CONTROL PERIOD

Of 74 animals 48 were controls for 3 months; 14 were controls from 2 to 2½ months; 5 were controls from 3¼ to 5 months; 7 were controls for 9 months.

In only 20, 8.9 per cent, of the 224 animals injected with the viable antigen was the organism recovered from the bile. It is therefore apparent that some time after the period of administration, recovery of the organism was relatively infrequent.

After preliminary injection of the viable organism and an appropriate rest period, the second group was submitted to vaccine treatment, as follows:

Vaccine Treatment

Adequate Diet, Planned Period—224 animals

In the group of 35 rabbits receiving *small dosages*, 19 received 26 or 27 treatments, 10 received 17 to 25 treatments, 6 received 28 to 35 treatments. Twenty-three were treated over a period of 3 months, 9 were treated from 2 to 2¾ months, 3 were treated 3¼ to 4½ months. The number of killed organisms given was as follows: 19 received single doses of 130,000 or 135,000 killed organisms; 9 received single doses of 33,000 to 57,000 killed organisms; 3 received single doses of 120,000 or 125,000 killed organisms; 4 received single doses of 140,000 to 189,000 killed organisms. A general average of 111,000 organisms per treatment was given.

TABLE III.—SUMMARY OF INCIDENCE OF CHOLECYSTITIS AND COEXISTENT LESIONS

Gross autopsy findings (1932–1940 experiments) full term, adequate diet	Control				Vaccine				Filtrate			
	74 animals				75 animals				75 animals			
	Lesion		Positive bile culture		Lesion		Positive bile culture		Lesion		Positive bile culture	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gall-bladder lesions, gross total	51	68.8	7	9.5	48	64	5	6.7	54	72	8	10.7
Gall-bladder lesions, questionable	3	4.1	—	—	15	20	—	—	6	8	—	—
Gall-bladder lesions, positive	48	64.7	7	9.5	33	44	5	6.7	48	64	8	10.7
Abnormal bile, total	24	32.4	—	—	19	25.3	—	—	26	34.7	—	—
Abnormal bile, questionable	5	6.8	—	—	1	1.3	—	—	5	6.7	—	—
Abnormal bile, positive	19	25.7	—	—	18	24	—	—	21	28.1	—	—
Normal bile with questionable gall-bladder lesions	3	4.1	—	—	11	14.7	—	—	4	5.3	—	—
Normal bile with positive gall-bladder lesions	24	32.4	—	—	19	25.3	—	—	25	33.3	—	—
No coexistent disease	5	6.8	2	2.7	4	5.3	—	—	9	12	—	—
No coexistent disease with questionable gall-bladder	—	—	—	—	2	2.7	—	—	1	—	—	—
No coexistent disease with positive gall bladder	5	6.8	2	2.7	2	—	—	—	8	10.7	2	2.7
Coexistent kidney lesions	9	12.2	2	2.7	6	8	—	—	6	8	1	—
Questionable gall bladder with positive kidney	—	—	—	—	1	—	—	—	1	—	1	—
Positive gall bladder with positive kidney	6	8.1	2	2.7	4	5.3	—	—	3	4	—	—
Coexistent joint lesions	19	25.7	2	2.7	18	24	—	—	18	24	1	—
Questionable gall bladder with positive joints	1	—	—	—	6	—	—	—	3	—	—	—
Positive gall bladder with positive joints	18	24.3	2	2.7	12	16	—	—	15	20	1	—
Coexistent joint and organic lesions	18	24.3	4	5.4	20	26.7	3	4	21	28	5	6.7
Questionable gall bladder with joint and organic lesions	1	—	—	—	5	6.7	—	—	—	—	—	—
Positive gall bladder with joint and organic lesions	17	23	4	5.4	15	20	3	4	21	28	5	6.7

In the group of 40 rabbits receiving *large or ascending dosage*, 19 received either 26 or 27 doses; 7 received 14 to 17 doses; 6 received 23 to 25 doses; 6 received 28 or 29 doses; 2 received 45 or 46 doses, or a general average of 26 doses. Twenty-eight received treatment for 3 months; 8 received treatment from 2 to 2¾ months; 4 received treatment for 4½ to 6 months. The number of killed organisms given was as follows: 18 received from 116,000 to 470,000 killed organisms; 20 received from 500,000 to 685,000 killed organisms; 2 received 1,358,000 or 2,312,000 killed organisms, or a general average of 516,000 killed organisms per dose.

The third group was submitted to filtrate treatment, as follows:

Filtrate Treatment

224 animals .

In the group of 40 rabbits given *small dosages*, 15 received 27 to 30 doses, 13 received 25 or 26 doses, 12 received 12 to 21 doses. Twenty-six received treatment for 3 months; 10 received treatment for 2 to 2¾ months, 4 received treatment for 3¼ months. The amount of filtrate given was: 23 received from 1.25 to 1.35 cubic centimeters, 11 received 0.60 to 1.05 cubic centimeters, 6 received 1.40 or 1.45 cubic centimeters.

In the group of 35 rabbits given *large or ascend-dosages*, 19 received 26 or 27 treatments, 11 received 14 to 25 treatments, 4 received 28 or 29 treatments, and 1 received 43 treatments. Twenty-six received treatment for 3 months, 8 received treatment for 2 to 2½ months, 1 received treatment for 5½ months. The amount of filtrate given was as follows: 14 received from 2.75 to 3.90 cubic centimeters, 13 received from 4.05 to 4.85 cubic centimeters, 7 received from 5.30 to 5.65 cubic centimeters, and 1 received 14.46 cubic centimeters.

TABLE IV.—GRADES OF GROSS GALL-BLADDER LESIONS OBSERVED

Grade	Control		Vaccine		Filtrate	
	No.	%	No.	%	No.	%
Negative	23	31.1	27	36	22	29.2
Plus-minus	3	4.1	15	20	6	8.
Plus 1	26	35.1	17	22.7	22	29.3
Plus 2	18	24.3	14	18.7	23	30.7
Plus 3	4	5.4	2	2.7	3	4

TABLE V.—INCIDENCE OF CHOLECYSTITIS WITH COEXISTENT LESIONS

Gross autopsy findings (1932–1940 experiments) full term, adequate diet	Vaccine								Filtrate							
	Small doses 35 animals				Ascending doses 40 animals				Small doses 40 animals				Ascending doses 35 animals			
	Lesion		Positive bile culture		Lesion		Positive bile culture		Lesion		Positive bile culture		Lesion		Positive bile culture	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gall bladder lesions, gross total	23	65.7	3	8.6	25	62.5	2	5	32	80	3	7.5	22	62.9	5	14.3
Gall-bladder lesions, questionable	9	25.7	—	—	6	15	—	—	4	10	—	—	2	5.7	—	—
Gall-bladder lesions, positive	14	40	3	8.6	19	47.5	2	5	28	70	3	7.5	20	57.2	5	14.3
Abnormal bile, total	8	22.8	—	—	11	27.5	—	—	16	40	—	—	10	28.5	—	—
Abnormal bile, questionable	—	—	—	—	2	5	—	—	2	5	—	—	4	—	—	—
Abnormal bile, positive	8	—	—	—	9	—	—	—	14	—	—	—	6	17.1	—	—
Normal bile with questionable gall bladder	7	20	—	—	4	10	—	—	2	5	—	—	2	5.7	—	—
Normal bile with positive gall bladder	8	22.8	—	—	11	27.5	—	—	14	35	—	—	11	—	1	—
No disease coexistent with gall-bladder lesions	1	2.9	—	—	3	7.5	—	—	6	15	—	—	3	8.6	—	—
No disease coexistent with questionable gall bladder	—	—	—	—	2	5	—	—	—	—	—	—	—	—	—	—
No disease coexistent with positive gall bladder	1	—	—	—	1	—	—	—	6	—	—	—	2	5.7	—	—
Coexistent kidney lesions	4	11.4	—	—	2	5	—	—	3	7.5	1	2.5	2	—	—	—
Questionable gall bladder with positive kidney	—	—	—	—	1	—	—	—	1	—	1	—	—	—	—	—
Positive gall bladder with positive kidney	3	—	—	—	1	—	—	—	1	2.5	—	—	2	5.7	—	—
Coexistent joint lesions	10	28.5	—	—	8	20	—	—	10	25	1	—	8	22.8	—	—
Questionable gall bladder with positive lesions	5	—	—	—	1	—	—	—	3	—	—	—	—	—	—	—
Positive gall bladder with positive joints	5	14.3	—	—	7	17.5	—	—	7	17.5	1	—	8	22.8	—	—
Coexistent joint and organic lesions	10	28.5	2	5.7	10	25.	1	2.5	13	32.5	2	5	8	22.8	3	8.6
Questionable gall bladder with joint and organic lesions	3	8.6	—	—	2	—	—	—	—	—	—	—	—	—	—	—
Positive gall bladder with joint and organic lesions	6	17.1	2	—	8	20	1	—	13	—	2	—	8	22.8	3	—

To ascertain the effect of treatment upon the pathologic picture, the data used to prepare Table I were appropriately distributed among the respective groups of 74 control, 75 vaccine treated, and 75 filtrate treated animals (Table III).

Necropsy of many hundreds of healthy rabbits, killed to obtain material for physiological and chemical studies, has given us an indelible picture of the healthy gall bladder in the rabbit. Likewise our experience with the experimental production of cholecystitis has taught us how to recognize grossly an unmistakably pathologic gall bladder. However, on some occasions during these experiments, necropsy revealed gall bladders that were not definitely pathologic, yet on the basis of our experience with normal gall bladders we were not justified in considering them negative. There were deviations from the normal, but the changes were too slight to characterize the organs as definitely diseased. In such cases we decided to record the observations as "plus-minus"; that is, the condition was intermediate between the normal and that clearly showing low grade pathology. Study of Table III discloses that the questionable, or "plus-minus," gall bladders furnish the crucial data when we seek to determine the efficacy of treatment in reducing the incidence of cholecystitis. If we consider the plus-minus lesions as belonging to the positive group, then the incidence of disease among the controls is 69 per cent, in the vaccine treated animals 64 per cent, and in the filtrate treated 72 per cent. These differences in frequency are too small to be of any worthy significance. On the other hand, if the plus-minus gall-bladder lesions are not considered, then the occurrence of definitely positive gall-bladder lesions for the control group is 65 per cent, while for the autogenous vaccine treated group it is 44 per cent, and for the filtrate treated group, 64 per cent.

Vaccine treatment, therefore, presumably lowered the incidence of gall-bladder disease by 21 per cent.

In regard to this difference, it is interesting to note that 20 per cent of the vaccine treated animals exhibited doubtful, or plus-minus, gall-bladder disease, while only 4 per cent of the controls and 8 per cent of the filtrate treated animals had plus-minus gall-bladder lesions. It is a question whether the observation of doubtful changes at the termination of treatment signifies that these lesions were in a state of involution or that a very low grade infection was persistent throughout the period of experimentation. In view of the low percentage of doubtful gall-bladder lesions among

TABLE VI.—RELATION OF GRADE OF GALL-BLADDER LESION TO METHODS OF TREATMENT

Grade of gross lesion	Vaccine				Filtrate			
	Repeated small doses 35 animals		Ascending doses 40 animals		Repeated small doses 40 animals		Ascending doses 35 animals	
	No.	%	No.	%	No.	%	No.	%
Negative	12	34.3	15	37.5	8	20	13	37.1
Plus-minus	9	25.7	6	15	4	10	2	5.7
Plus 1	8	22.8	9	22.5	15	37.5	7	20
Plus 2	6	17.1	8	20	12	30	11	31.4
Plus 3	0	0	2	5	1	2.5	2	5.7
Total definite lesions	14	40	19	47.5	28	70	20	57.1
Total of all lesions, including definite and plus-minus	23	65.7	25	62.5	32	80	22	62.9

the controls we feel that the evidence points more strongly to the assumption that these were in process of involution.

Failure with the filtrate treatment may be ascribed either to inadequate dosage or to inability of the viable organism to elaborate a potent exotoxin.

Table IV is a frequency distribution of the various grades of gall-bladder disease observed in the 3 groups (control, vaccine treated, and filtrate treated animals).

Comparison of the control and vaccine treated groups discloses: (1) that there were 5 per cent more negative gall bladders in the vaccine group; (2) there were 12.4 per cent fewer mildly positive (plus 1) gall-bladder lesions in the vaccine group; (3) there were 5.6 per cent fewer moderately severe (plus 2) gall-bladder lesions in the vaccine group. The incidence of severe (plus 3) gall-bladder lesions were too few to lend themselves readily to interpretation. Yet if one adds the 5 per cent difference in the incidence of negative gall bladders in the control and vaccine groups to the 16 per cent difference in the doubtful lesions for the control and vaccine groups, the resulting sum equals the sum of the respective differences in plus 1, plus 2, and plus 3 lesions of the control and vaccine treated gall bladders; e.g., in the negative group there was a difference in percentages of control and vaccine of 5 per cent; in the plus-minus group of 16 per cent or a total in these 2 groups of 21 per cent. In the plus 1 group the difference was 12.4 per cent, in the plus 2 group the difference was 5.6 per cent, in the plus 3 group the difference was 2.7 per cent or a total of 20.7 per cent in the latter 3 groups.

Repeated small doses and ascending doses were employed in order to evaluate the merits of the two methods of treatment. The data obtained with the respective groups after the small and the ascending doses were used are presented in Table V. Here again evaluation of the improvement in the gall-bladder lesion depends upon what significance is to be placed upon the doubtful lesions.

The frequency of the respective grades of gall-bladder lesion in relation to the mode of dosage with vaccine or filtrate is presented in Table VI, an extension of Table IV.

The total positive culture recovery of the control, vaccine treated, and filtrate treated groups is given in Table VII.

In Table VIII the incidence of various grades of gross gall-bladder lesions observed at necropsy is compared with the number of injections of viable antigen 7 (Streptococcus nonhemolyticus) given during the infective phase of the experiment.

The question may be raised as to whether the number of injections (amount of viable culture) given eventually determines the degree of gall-bladder lesion produced. To ascertain accurately the effect of a number of injections, an equal num-

TABLE VII.—TOTAL POSITIVE CULTURE RECOVERY

Source	Control 74 animals		Vaccine 75 animals		Filtrate 75 animals	
	No.	%	No.	%	No.	%
Animals with positive culture	15	20.2	8	10.7	14	18.7
Gall-bladder wall, bile negative	1	9.5	5	6.7	8	10.7
Bile	6					
Joints	6	8.1	2	2.7	8	10.7
Liver	2		2		4	
Kidney	1		1		1	
Urine	1		2		4	
Cyst, omental	1					
Total positive cultures	18	24.3	12	16	25	33.3

TABLE VIII.—FREQUENCY OF VARIOUS GRADES OF GROSS GALL-BLADDER LESIONS NUMBER OF INJECTIONS OF VIABLE ANTIGEN

No. of injections (each averaging 0.05 cc.)	Frequency of lesions				
	Negative	Plus-Minus	Positive 1	Positive 2	Positive 3
1 to 10	30 1*	8	29	20	3
11 to 20	13	8	14	16	4
21 to 30	8	4	11	9	2
31 to 40	8	2	4	7	0
41 to 50	9	1	4	1	0
51 to 60	2	1	3	2	0

*Additional animal in which gall bladder was congenitally absent.

ber of animals should have been used for each range of injections, which, unfortunately, was not done. Table VIII shows, for example, that only 8 rabbits received injections in the range of 51 to 60, while 91 rabbits received injections in the range from 1 to 10. Since the average number of injections of culture given in our experiment was 18 for each group, it is not surprising that 146 (65 per cent) of the animals received injections in the 1 to 20 range. However, severe (plus 3) lesions were not found in any group when more than 30 injections of the viable antigen were given.

The average life expectancy for a rabbit is about 6 years (312 weeks). The period of inoculation with antigen 7 averaged 10 weeks, or 1/30 (10/312) of a rabbit's life. With 60 years as the life expectancy of man, then by direct comparison the human being would have been subject to an active infection for 2 years. Most of the rabbits received vaccine or filtrate for 3 months, or 1/26 (12/312) of their lives. For the human subject this period of treatment would be comparable to 2.3 years.

CONCLUSIONS

1. A final survey is presented of experimental cholecystitis produced in rabbits by the intravenous injection of a viable strain of nonhemolytic streptococcus originally obtained from a patient suffering from cholecystitis and colitis.

2. After an initial period of inoculation with the viable organism and a subsequent rest period, the animals were divided into 3 groups, one maintained as the control, the second treated with vaccine, and the third with a filtrate prepared from the same organism.

3. By the use of a modified technique the incidence of cholecystitis was increased in this series to 68 per cent.

4. The gross findings at necropsy were classified as (a) doubtful; (b) plus 1; (c) plus 2; and (d) plus 3. Any difference observable was in favor of the animals who received vaccine treatment. Of the control group, 64.7 per cent were definitely positive and 4.1 per cent doubtful; of the vaccine group, 44 per cent were positive and 20 per cent doubtful; and of the filtrate group, 64 per cent were positive and 8 per cent doubtful. The observation of doubtful lesions at the termination of treatment may signify a state of involution or the persistence of a low grade infection. In view of the small percentage of doubtful gall-bladder lesions among the controls we feel that the evidence favors the assumption that the doubtful lesions were undergoing involution. The total positive culture recovery was a somewhat lower number.

5. On the other hand, in a general survey, the evidence of gall-bladder damage was markedly constant in all three groups, attesting to the fact that the viable organism was responsible for the changes. No evidence of gross or microscopic change was found in 9 normal rabbits selected from stock.

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2. REHFUSS, M. E., and NELSON, G. M. Am. J. Digest. Dis., 1934–35, 1: 759.

EDITORIALS

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MISUSE OF MORPHINE AS A THERAPEUTIC AGENT

IN anybody's list of the drugs that are most useful in medicine, morphine would be placed near the top. Misuse of the agent that may have occurred in military medicine only points to a similar although perhaps less noticeable abuse in private practice, for military medicine during wartime represents a cross section of civilian medicine. Both pharmacologists and clinicians say that the misuse of morphine is not to be placed at their respective doors. Where the responsibility lies for the unwise employment of this agent is less important than the fact. It is to be recognized too that here is one more example of the regrettable state into which the teaching of therapeutics has fallen. The situation is a paradoxical one in that medical schools and hospitals whose aim is to provide a background which will permit the student to understand the treatment of disease, often fail to accomplish this reasonable end. At least they fail, have failed in the present instance, to ensure the sensible use of this most important agent.

Aside from the fact that adequate teaching of therapeutics does not exist in many medical centers, the causes of morphine overdosage (for its misuse is chiefly that) are several.

There is failure to appreciate that nearly the safe maximum analgetic effect of morphine can be produced by 15 milligrams (gr. ¼) and that 30 milligrams (gr. ½) can produce serious depression in small individuals or in any individuals whose tolerance may have been lessened by wounds, particularly those associated with hemorrhage or pneumothorax or other disability that limits the intake and distribution of oxygen. In civil life everybody, practically, knows that morphine is contraindicated in hypothyroidism and is dangerous in obstetrics. Too few know that impaired liver function increases the danger that an otherwise modest dose may become an overdose in a given case.

Failure to realize that subcutaneous injections of morphine will be only poorly absorbed, if at all, when the peripheral circulation is sluggish or inactive, as a result of cold or low systemic blood pressure, has led to rather frequent trouble. Failure to get pain relief from the unabsorbed morphine leads to the administration of a second or third dose, all of which may be absorbed at one time when the peripheral circulation is reestablished as a result of resuscitative measures.

The incorrect belief that extensive wounds are inevitably associated with severe pain often leads to needless use of morphine. At Anzio, only a quarter of the severely wounded patients said, in response to a direct question,

that they were having enough pain to want pain relief medication. This was in one of the most forward hospitals and these patients had not had morphine for seven hours on the average.

The administration of morphine for conditions that will not respond satisfactorily to the agent, however large the dose, is a common error. Specifically, the use of morphine to treat the restlessness associated with bleeding, with anoxia, or with hysteria cannot be soundly defended. The use of morphine in shock, except for the treatment of severe pain, is contraindicated: it produces sweating, it causes nausea and vomiting. Thus it not only increases fluid loss but makes the intake of fluids by mouth and their retention often impossible.

Morphine is occasionally administered where other agents (barbiturate sedation, for example) are far better, as in the treatment of "nervousness," "the jitters," sleeplessness. Individuals with these problems are of course likely candidates for addiction. The use of morphine as a routine in preanesthetic medication is difficult to justify, for there is reason to believe that the patient pays too high a price for the depression obtained by means of this agent, and that the effect desired could be achieved better in other ways.

The evidence is mounting that morphine has a single legitimate use: the relief of severe pain—a widely accepted view, but one too little put into practice.

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THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

As in previous years, *The 1944 Year Book of Radiology*[1] offers abstracts of articles appearing in the world's literature during the period from about the middle of the preceding year (1943) to the middle of the current year (1944). The value of such a volume is greater now during the period of war than ever to conserve the time and energy of the war weary doctor. By thumbing through the pages, the busy physician can with little effort acquaint himself with the advances and refinements in both interpretation and treatment. In collecting the material, the editors have covered the publications of the world, abstracting 435 leading articles from the United States and 12 foreign countries.

The volume of 450 pages, with 363 excellent illustrations is well printed and bound. A comprehensive index is appended.

The "practice quiz" of 20 questions listed on the jacket is intriguing and stimulating.

Dr. Waters has followed the excellent plan of classifying the articles on diagnosis by body systems. The articles abstracted are well chosen and adequately illustrated. Dr. Kaplan has reviewed the field of radiotherapeutics in an introduction of 40 pages followed by his usual excellent abstracts of well chosen articles. Physicians who own previous volumes look forward yearly to its publication and will make certain that their series is complete. To those not familiar with the excellent book, it is recommended without reservation as a valuable addition to your medical library. EARL E. BARTH.

IN the volume entitled *The Gastro-intestinal Tract; a Handbook of Roentgen Diagnosis*[2] by Fred Jenner Hodges which is one of a series of handbooks of roentgen diagnosis being published by the Year Book Publishers, the author has drawn from his wide experience with a wealth of material at the University of Michigan Medical School and has done an admirable job of covering the field of gastrointestinal roentgenology.

The subject matter is divided into six sections: the esophagus, the upper gastrointestinal tract, the biliary tract, the colon, the abdomen generally, and findings of particular interest. The importance of preliminary fluoroscopy, methods of examination, accurate recording of findings, and plans of cataloging are described in the introduction.

The arrangement of placing the description and legends on the left hand page and the illustration on the opposite side facilitates study. The illustrations are numerous, well chosen, and are grouped in such a manner that several illustrative roentgenograms of the same patient appear side by side. All of the 604 illustrations are in the negative phase and excellently reproduced. A short bibliography appears at the end of each section and an adequate index is appended.

The author and publishers have succeeded admirably in the production of an excellent handbook. It is lucid, concise, surprisingly comprehensive for its size, and can be highly recommended to students, roentgenologists, gastroenterologists and to any physician interested in the diagnosis of the diseases of the gastrointestinal tract. EARL E. BARTH.

THE very excellent book *The Art of Resuscitation*[3] by Paluel J. Flagg treats in a most complete fashion the subject of resuscitation. The foreword is written by Chevalier Jackson. The beginning chapters relate the growth of the art of resuscitation from the history of tracheotomy and intubation through the efforts of organizing a society for the prevention of asphyxial death to its present status. Asphyxia is next treated as a generic problem. The experimental physiology involved is accurately and well defined. The principles of resuscitation are set forth with clarity and simplicity with the correct stress on indication for treatment and types of treatment. The methods of resuscitation are enumerated with emphasis on intratracheal insufflation. A chapter is devoted to the transportation of the unconscious patient. The author describes in detail the reconstruction of a commerical ambulance to take care of the unconscious patient, provide suction, continuous oxygen, and intravenous infusions when necessary. He devotes part of his book to a careful thorough discussion of asphyxia as a specific problem in the newborn, from high altitudes, from carbon monoxide poisoning, from submergence, in anesthesia, in poliomyelitis, in electrocution, in cases encountered in fire fighting and mechanical obstruction of respiration, from the pathological obstruction of respiration and from clinical disease. Each phase of this part of the book is amply illustrated and is unfolded with the expertness that only a man with Dr. Flagg's vision and experience could handle.

In another section the committee of asphyxia of the American Medical Association enumerates the

[1] THE 1944 YEAR BOOK OF RADIOLOGY. DIAGNOSIS edited by Charles A. Waters, M.D., and Whitmer B. Firor, M.D. THERAPEUTICS edited by Ira I. Kaplan, B.Sc., M.D. Chicago, Ill.: The Year Book Publishers, Inc., 1944.

[2] THE GASTRO-INTESTINAL TRACT; A HANDBOOK OF ROENTGEN DIAGNOSIS. By Fred Jenner Hodges, B.S., M.D. Chicago: The Year Book Publishers, Inc., 1944.

[3] THE ART OF RESUSCITATION. By Paluel J. Flagg, M.D. New York: The Rheinhold Publishing Corp., 1944.

fields in which immediate attention is needed. A method is outlined of attacking the problem by public education, research, and postgraduate instruction of physicians. Emphasis is made on the rôle of the United States Public Health Service in first aid and safety. The important phases of asphyxia are brought up-to-date by lengthy discussion of the Army problem. An adequate discussion of commercial warfare and its relation to asphyxia is treated extensively, and preventive treatment is outlined. Other subjects covered with thoroughness include asphyxia in dentistry, in civilian defense, and as an economic department of public health service. All forms of gas therapy are co-ordinated.

The purpose of this book is an intensely practical one. It is an attempt based upon more than 25 years of intimate experience with the unconscious patient to tell the reader what to do when faced by an acutely axphyxiated patient about to die. The book is a complete treatise on the subject, treating every phase connected with asphyxial anoxia with intelligence. It will fill the much needed place in the library of the progressive physician. MARY KARP.

IN a nicely printed and well organized monograph, Dr. H. F. Moseley has produced a needed work on the disease of the shoulder. The monograph *Shoulder Lesions*[1] contains an up-to-date concept of the pathology in the shoulder region in the extremely short space of 181 pages.

The subject is presented in chapters which may be read independently, making for ready reference. Thirty case reports are included illustrating the diagnosis and treatment of the various lesions discussed. The book covers ruptures of the rotator cuff, dislocations, calcified deposits, periarthritis, the bicipital syndrome, x-ray diagnosis and treatment, operative treatment and restoration of shoulder function. Of particular interest is the chapter on neurological aspects of shoulder pain written by Dr. F. L. McNaughton.

The discussion of shoulder mechanics and examinations is much too brief, and thus loses much of its value to the reader.

On the whole, this book by Dr. Moseley, presents the subject of shoulder lesions in a concise readable form while a detailed account of the debated points of pathology is avoided.

WILLIAM A. LARMON.

[1]SHOULDER LESIONS. By H. F. Moseley, M.A., D.M., M.Ch. (Oxon.), F.R.C.S. (Eng. and C.), F.A.C.S. Springfield, Ill.: Charles C. Thomas, 1945.

CORRESPONDENCE

DICUMAROL THERAPY IN POSTOPERATIVE THROMBOPHLEBITIS AND PHLEBOTHROMBOSIS— A Correction

OPPORTUNITY has been given me by the Editors of SURGERY, GYNECOLOGY AND OBSTETRICS to correct a statement as written in the manuscript for my article, entitled "Dicumarol Therapy in Postoperative Thrombophlebitis and Phlebothrombosis" which appeared in the July, 1945 issue. The sentence beginning in line 1, page 81, should read as follows: "Their policy is to use 35 seconds as an arbitrary standard; when the prothrombin time is longer than 35 seconds, dicumarol is *omitted*, and when it is less, the drug is *administered*. WILLARD H. PARSONS.

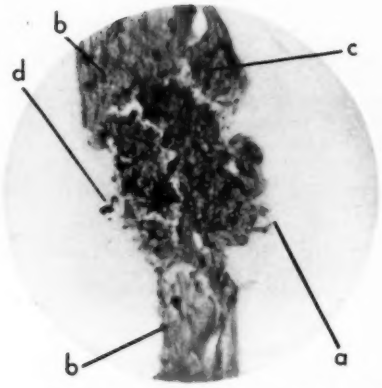

Fig. 2. Case 1, No. 47890. Pathological lesion, *a*, with cortical bone, *b*, on either side with vascular osteogenic type connective tissue infiltrating interstices, *c*, of cortical bone. Cortex destroyed by new-growth at *d*. ×21.

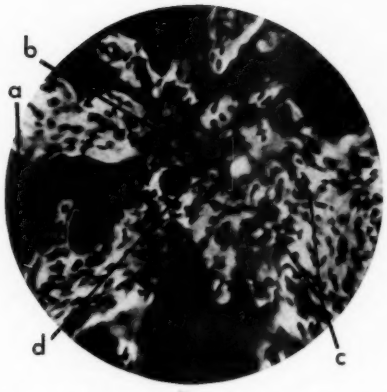

Fig. 3. Case 1, No. 47890. This section shows a calcified osteoid, *a;* osteoid, *b;* vascular cellular osteogenic connective tissue with numerous osteoblasts at *c;* and one osteoclast at *d*. ×358.

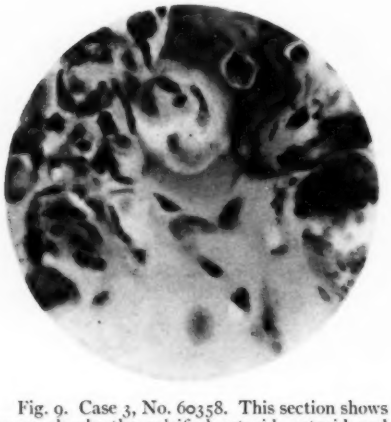

Fig. 9. Case 3, No. 60358. This section shows more clearly the calcified osteoid, osteoid and vascular cellular osteogenic connective tissue along with two osteoclasts and numerous osteoblasts. ×833.

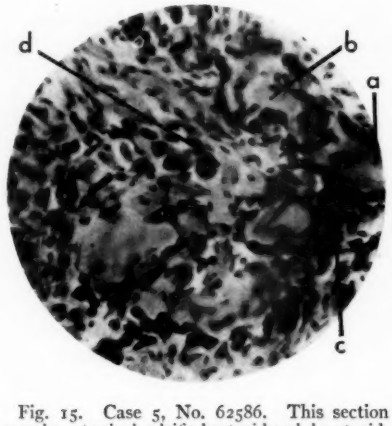

Fig. 15. Case 5, No. 62586. This section reveals, *a*, typical calcified osteoid and, *b*, osteoid, lying in a vascular cellular osteogenic mesenchyme in which there are numerous, *c*, osteoblasts and, *d*, osteoclasts. ×358.